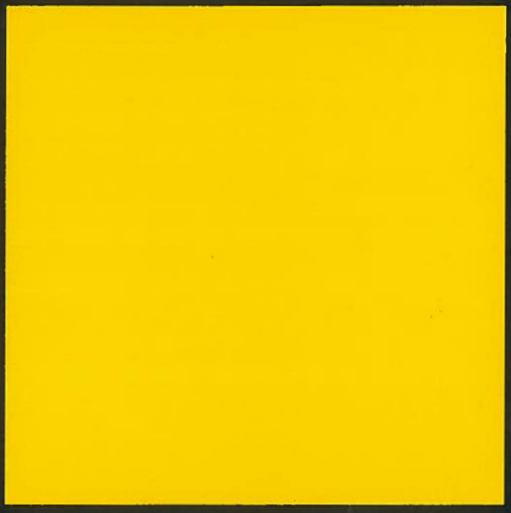
Therapy and prevention of winter depression. The importance of the timing of the exposure to light

Meesters, Ybe

THERAPY AND PREVENTION OF WINTER DEPRESSION

The Importance of the Timing of the Exposure to Light



Ybe Meesters

THERAPY AND PREVENTION OF WINTER DEPRESSION

The Importance of the Timing of the Exposure to Light

STELLINGEN

behorende bij het proefschrift

THERAPY AND PREVENTION OF WINTER DEPRESSION
The Importance of the Timing of the Exposure to Light

Ybe Meesters

1. Er zijn aanwijzigingen dat na een vroegtijdige lichtbehandeling bij winterdepressieve patiënten ernstige klachten gedurende de rest van het seizoen uitblijven. *(dit proefschrift)*

2. Zolang een Nederlandse civiele rechter nog als stakingsbreker kan fungeren, bestaat er in dit land klassejustitie.

3. De invloed van persoonlijkheidsfactoren op de effecten van lichtbehandeling verdient meer aandacht.

4. Het is een wonderlijk fenomeen dat een coalitiekabinet zonder katholieke inbreng zich tooit met de kleur paars.

5. De oorspronkelijke opvatting dat winterdepressie zou kunnen worden opgevat als een analogon van winterslaap is, gezien de huidige stand van kennis, moeilijk te handhaven.

6. Sommige ethici vervullen in de huidige tijd de functie die de kerk in vroeger eeuwen had: zonder enige rationele en empirische onderbouwing doen zij uitspraken over morele kwesties. Het is verbazingwekkend en tegelijk beangstigend te merken dat er net zo serieus naar deze mensen wordt geluisterd als vroeger naar de voorgangers in de kerk.

7. Het verband tussen het vóórkomen van winterdepressie en breedtegraad is twijfelachtig.

8. Privatisering van het ophalen van huisvuil leidt tot illegaal storten.

9. De investering in menskracht en geld ten bate van de regelgeving in zake het milieu staat vaak in geen verhouding tot haar effecten op het milieu.

10. De resultaten van epidemiologisch onderzoek naar de puntprevalentie van depressiviteit worden beïnvloed door het seizoen van dataverzameling.

11. De regel dat een psychiater eindverantwoordelijke is voor een door een psycholoog uitgevoerde behandeling is meer gebaseerd op macht dan op kennis.

12. Het is opmerkelijk dat dezelfde regering die in het buitenland ongevraagd staat te dringen om bij rampen en in oorlogssituaties - al dan niet militaire - hulp te bieden aan de zwaksten van de samenleving, in eigen land zo weinig prioriteit geeft aan de geneeskundige zorg voor de zwakkeren in de samenleving.

13. Als men in een advertentie de voorkeur uitspreekt voor de benoeming van een vrouw, betekent dat dat men bij voorkeur geen man benoemt.

14. Als voor de overheid hetzelfde uitgangspunt zou gelden als bij de nieuwe voorstellen voor de studiefinanciering, waarbij een verstrekte beurs bij het niet op tijd afronden van die taakstelling moet worden terugbetaald aan de geldgever, dan zou die overheid genoodzaakt zijn om veel geld terug te sturen naar de belastingbetaler.

15. Voor de informatievoorziening van het publiek is het wenselijk dat journalisten meer geïnteresseerd zouden zijn in het onderwerp waarover zij berichten dan in de ruimte die zij ermee dienen te vullen.

16. Blijkens de reglementen dienen zes stellingen geen betrekking te hebben op het proefschrift. Zij dienen wetenschappelijk verdedigbaar te zijn. In dit licht gezien getuigen nogal wat stellingen in proefschriften van een grove overschatting van de mogelijkheden van de wetenschap en de capaciteiten van de promovendus en de promotor.

Groningen, 10 oktober 1994

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The Importance of the Timing of the Exposure to Light

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op gezag van de
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te Oosterwolde -Fr-

Promotor: Prof. Dr. R.H. van den Hoofdakker

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Prof. Dr. A. Wirz-Justice, Psychiatrische Universitätsklinik Basel

"We can easily forgive a child who is afraid of the dark.
The real tragedy of life, is when men are afraid of the light"
(text from place-mat at Julian Café, Julian CA, USA)

aan:
Josie
Sjoerd en Alie

Paranimfen: Jaap Jansen
Jan Werkman

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CONTENTS

Chapter I

INTRODUCTION

The recognition of the impact of the seasons is not new in medicine. As early as around 400 BC Hippocrates described seasonal influences on diseases (Wehr, 1989). The first patient we know from medical literature suffering from seasonal affective disorder (SAD) is Lady Ann Grenville, who lived from 1642 to 1691. Descriptions of seasonal affective disorders have appeared ever since, such as those by Pinel in 1806. Kasper (1991) mentions 11 descriptions of SAD during the 19th and 20th century (until 1980).
The first systematic description of SAD was published by Esquirol in 1845, together with some epidemiological data. Like Hippocrates, he recognized the influence of the physical surroundings and the seasons on the course of mood. He prescribed a stay in Italy during the winter months to a patient who lived in Belgium in order to prevent a winter depression. The first person to relate a shortage of light to mood changes was the ship's surgeon Cook while going on an expedition to Antarctica in 1898 (Jefferson, 1986). The first case study describing the treatment of mood disturbance with artificial light is by Marx (1946). He administered 'sun-ray treatment' to mood disturbed soldiers, who were staying in the North of Scandinavia during the Second World War.
The early developments in modern light treatment for seasonal affective disorder were greatly influenced by Herbert Kern. Mr. Kern suffered from seasonal mood disturbances. After registering his mood over the years, he concluded that there must be a relation between the seasons and his mood. As a scientist, he discussed his complaints and views with photo-biologists and a psychiatrist (Dr Mueller), and he also contacted the National Institute of Mental Health (NIMH), where Lewy et al. had just discovered the possibility of suppressing the human production of melatonin with bright light of high intensity (Lewy et al., 1980). With the scientists of the NIMH, Kern participated in an experiment which exposed him to artificial bright white light, whereupon his mood disturbances disappeared (Lewy et al., 1982, Rosenthal et al., 1983). In the same winter, Mueller found similar positive results in another patient (Mueller and Allen, 1984; Rosenthal et al., 1984). After these encouraging results, the researchers of the NIMH developed an experimental design exposing 29 SAD patients to light. The results were published in the classic paper by Rosenthal et al., 1984. In the same publication the diagnostic criteria for seasonal affective disorder were formulated. Replicating the therapeutic effects of the administration of artificial bright light has triggered increasing attention of researchers and physicians ever since.

Table 1. Criteria for winter depression

Seasonal affective disorder Rosenthal et al. 1984	Seasonal pattern DSM-III-R (1987)	Seasonal pattern DSM-IV Draft (1993)
		specify if: With seasonal pattern(can be applied to Bipolar I Disorder, Bipolar II Disorder, and Major Depressive disorder Recurrent):
A. A history of major affective disorder, according to the RDC (Spitzer et al., 1978).	A. There has been a regular temporal relationship between the onset of an episode of Bipolar Disorder (including Bipolar Disorder NOS) or Recurrent Major Depression (including Depressive Disorder NOS) and a particular 60-day period of the year (e.g., regular appearance of depression between the beginning of October and the end of November).	A. There has been a regular temporal relationship between the onset of an episode of Bipolar I or Bipolar II Disorder or Major Depressive Disorder, Recurrent, and a particular time of the year (e.g., regular appearance of depression in the fall or winter).
B. At least two consecutive years in which the depressions have developed during fall or winter and remitted by the following spring or summer (a history of this pattern changing with changes in latitude or climate would strengthen the diagnosis).	B. Full remissions (or a change from depression to mania or hypomania) also occurred within a particular 60-day period of the year (e.g., depression disappears from mid-February to mid-April).	B. Full remissions (or a change from depression to mania or hypomania) also occur at a characteristic time of year (e.g., depression disappears in the spring.
C. absence of any other axis I psychiatric disorder.	C. There have been at least three episodes of mood disturbance in three separate years that demonstrated the temporal seasonal relationship defined in A and B; at least two of the years were consecutive.	C. In the last two years, two episodes have occurred that demonstrate the temporal relationship defined in A and B, and no nonseasonal episodes have occurred during that same period.
D. the absence of any clear-cut seasonally changing psychosocial variability in mood and behaviour, eg, work, stresses.	D. Seasonal episodes of mood disturbance, as described above, outnumbered any nonseasonal episodes of such disturbance that may have occurred by more than three to one.	D. Seasonal episodes of mood disturbance, as described above, substantially outnumber any nonseasonal episodes of such disturbance that may have occurred over the individual's lifetime.

The Syndrome

Winter depression is now defined as a mood disturbance with an onset of symptoms in the fall/winter followed by spontaneous recovery in spring/summer. Decreased activity and dysphoria are often accompanied by lack of concentration, decreased energy, irritability, anxiety, decreased libido and social withdrawal (Oren and Rosenthal, 1992). To diagnose the syndrome, two main sets of criteria are used, i.e. the Rosenthal criteria (1984) and the DSM-III-R criteria (1987) (see Table 1.).
Since 1984 most researchers have used the criteria formulated by Rosenthal et al. With its inclusion in the Diagnostic and Statistical Manual of Mental Disorders (DSM III-R, APA, 1987), the syndrome was accepted by the psychiatric community. The DSM-III-R criteria differ slightly from Rosenthal's (see Table 1.). One of the main differences concerns the timing of onset and termination of the syndrome. In DSM-III-R a 60-day window is defined within which complaints should develop, and another 60-day window in which they should disappear. Other discrepancies concern numbers and sequences of episodes. There has been some discussion about the surplus value of these limitations for research. The Rosenthal criteria have been shown to have sufficient predictive power while none of the DSM-III-R criteria appear to have any additional value (Dittmann et al.,1992). Therefore, most researchers have used the less strict criteria of Rosenthal et al. (1984), which is exactly what we did in our first studies. In view of the increased use of DSM-III-R criteria in scientific publications, both sets of criteria were applied in the last study of this thesis (chapter IV).
In recent drafts of DSM IV, the syndrome is still a separate entity (Bauer, 1993). The 60-day window criterion has been removed. Nevertheless, there are still some doubts as to wether the new version of DSM represents the best description of the syndrome, with the exclusion of the combination of seasonal pattern with recurrent mood disorders other than Bipolar I and II or Major Recurrent depression being particularly criticized (Rosenthal and Terman, 1993).

In most patients suffering from SAD, the symptoms do not recur every winter (Rosenthal et al., 1984). Without prophylaxis or treatment, about two thirds of SAD subjects become depressed in the following winter (Thompson, 1989; Meesters et al., Chapter V).
Apart from the characteristics of the time course mentioned above, winter depressives

frequently show 'atypical' complaints (i.e. atypical for depression), such as increased fatigue, hypersomnia, increased appetite, carbohydrate craving, and weight gain. For the assessment of these, Rosenthal and Heffernan (1986) developed seven questions which they added to the Hamilton Rating Scale for Depression (HRSD, Hamilton, 1967). This adapted version of the classic standardized clinical interview is widely used to assess the severity of winter depression. In addition to this instrument, we also applied the Beck Depression Inventory (BDI, Beck et al., 1961; 1979; Bouman et al., 1985). As the BDI is a self-rating scale, it is more appropriate for longitudinal measurements. We therefore used it to monitor the course of mood of the patients during the entire winter season. In order to assess the atypical complaints, we added a number of additional items to the BDI. The relationship between the atypical scores on the extended BDI and the atypical scores on the adapted version of the HRSD is described in chapter II.

Prevalence

Some studies suggest that the prevalence of SAD depends on geographic latitude. Lingjaerde et al. (1986) found significantly more feelings of depression in the northern of Norway than in the southern part. In the USA, Potkin and coworkers (1986) found a highly positive correlation between SAD and latitude. The prevalence figures for Alaska (Booker and Hellekson, 1992) are much higher than those for Maryland (USA) (9.2% and 4.3% respectively; Kasper et al., 1989). Rosen et al. (1990) found prevalence rates for Nashua (New Hampshire): 9.7%, New York: 4.7%, Montgomery County (Maryland): 6.3% and Sarasota (Florida): 1.4%).

In Europe there are some indications as well that latitude is important: the prevalence figures for Iceland (Magnusson and Stefanson, 1993) and Finland (Hagfors et al., 1992) are higher than those for Switzerland (Wirz-Justice et al., 1992)(3.8%, 3.4% and 2.2%, respectively), although these figures suggest smaller differences than those reported in the USA. Some studies fail to support the possible relationship between latitude and prevalence. While the prevalence of SAD in Iceland is 3.8% (Magnusson and Stefansson, 1993), only 1.2% of the population of descendants of Icelandic emigrants in Canada appears to be affected (Magnusson and Axelsson, 1993): both rates are lower than those reported from the east coast of the USA. An Italian study showed a prevalence of 7.4% (Muscettola et al., 1990), while Partonen et al. (1993) did not find a relationship between

latitude (60N-70N) and prevalence in Finland. These data show that the role of latitude is still unclear, and that other factors may be involved. Magnusson and Axelsson (1993) suggest that the smaller figures for the population in Iceland and their descendants in Canada might be due to a genetic adaptation of the former population as compared to those for the population of the USA. In view of these data, the prevalence in The Netherlands is hard to predict. If latitude plays some role, an estimation of 2-5% for The Netherlands would be reasonable. An ongoing epidemiologic study in Groningen will soon provide detailed information.

Treatment

Light exposure has been shown to be a very effective treatment for winter depression (Terman et al., 1989; Rosenthal and Wehr, 1992). Improvement after light therapy usually takes 2-4 days (Rosenthal et al., 1985).

The effects of medication have been less well studied. In a controlled study, treatment with d-Fenfluramine has been shown to be highly effective (O'Rourke et al., 1989). Ruhrmann and Kasper (1992) mention some antidepressants which might be of use, but, these impressions are based on case studies or studies with very small sample sizes. In open trials promising results were found after treatment with Tranylcypromine or Bupropion (Dilsaver and Jaeckle, 1990; Dilsaver et al. 1992). In a longitudinal single case study Wirz-Justice et al. (1992) found that their patient responded both to light and citalopram. The time course of improvement differed, however: on light treatment response developed within 3-4 days, on citalopram within two weeks.

Usually, patients prefer light over drugs. Drugs take more time to elicit beneficial effects and cause aversive side-effects (Oren and Rosenthal, 1992). Although combinations of light exposure and antidepressants have been applied, and some clinicians have observed better symptomatic improvement on the combination than on either of these treatments alone (Rosenthal, 1993a), some caution has to be exercised. Wang et al. (1992) described an increased risk in light damage to lens and retina on the administration of antidepressant/neuroleptic medication and light. The possibility that the addition of drugs is the crucial factor is all the more real in view of the fact that without medication no

ophthalmological damage or abnormalities were found even after the use of high intensity light (10,000 lux) (Terman et al., 1990).
Although light treatment is the first choice of treatment, other kinds of antidepressive treatment such as stress management, psychotherapy and cognitive and behaviour therapy are also used in treating winter depressions (Rosenthal, 1993b).

Hardly any relapses were found if light is administered at the very beginning of the depressive episode. If the depression is treated at a later stage, relapse rates show a large variety, ranging from a few days to several months or no relapse at all. No data are available on relapse rates after drug treatment.

Hypotheses

The mechanisms underlying the beneficial effects of light treatment are far from clear. Existing theories encompass hypothesized mechanisms at virtually every level of functioning, from the behavioral to the molecular (Rosenthal and Wehr, 1992). They will not be enumerated here, as they are of little direct relevance in the context of this thesis. There is one exception, however: a chronobiological hypothesis postulated by Lewy et al. (1987,1988), known as the phase delay hypothesis. According to this hypothesis winter depression is caused by abnormal phase relations between the circadian clock and the sleep/wake cycle. In most cases the clock is thought to be delayed, in a minority of cases advanced. It has been shown that light in the morning can phase advance circadian rhythms (Czeisler et al., 1989; Dijk et al., 1989; Minors et al., 1991), while evening light delays them. The authors claim to have found supportive evidence for their hypothesis. They reported that in most of their patients morning light was therapeutically superior to evening light, while in a minority the opposite was found. They even observed indications that therapeutic effects might be related to normalization of baseline circadian abnormalities (Lewy et al., 1987, 1988; Sack et al. 1990)

Aim of the Thesis

Lewy et al.'s findings, however, have never been convincingly replicated, as will be discussed in later chapters. The issue of the involvement of circadian phase disturbances in

winter depression is controversial (Blehar and Lewy, 1990) and so is the issue of the importance of the timing of light treatment. Nonetheless, both the seasonal timing of the syndrome and it's susceptibility to light treatment strongly suggest that some chronobiological mechanisms might be implicated. A better understanding of these mechanisms is of major theoretical and practical importance, and would have important implications for treatment and prevention. Therefore, this thesis is dedicated to the investigation of the importance of the timing of light treatment with respect to the time of day, and to the onset of a new SAD episode.

Daily Timing of Light Treatment

A comparison was made between the clinical effects of light treatment in the morning and light treatment in the evening. For that purpose, bright light (2500 lux) was administered to two groups of patients during 3 hours, on 5 consecutive mornings, respectively evenings. In this study (described in chapter III) morning light and evening light were equally effective. After that, the effects of five one-week treatment protocols were compared (described in chapter IV): morning light only, afternoon light only, evening light only, morning light followed by evening light and evening light followed by morning light. Again, no significant differences were found between the treatment modalities, indicating that neither timing, nor differences in rank order of light exposure are of any importance to the outcome of light treatment. It should also be mentioned that in the latter study light intension was much higher (10,000 lux) and exposure was much shorter (30 minutes) than in the former study. The therapeutic results turned out to be the same. The practical conclusion is that patients can be successfully treated by short sessions at convenient times of the day.

Timing of Light Treatment in Relation to the Onset of a New Depressive Episode

Since winter depressions recur, it would be highly desirable to develop preventive means. We approached this issue in two ways. In one study (described in chapter V), patients were monitored every week, starting in the summer, while they were still symptom-free. After the development of the first (mild) signs of depression in one group of these patients, light treatment was administered, while another group was left untreated until a depression had

fully developed. Virtually all patients who had been treated remained well during the rest of the season, whereas nearly all of the control patients became clearly depressed. The positive results of this study inspired us to perform another trial in which light treatment was administered at the beginning of autumn before there were any depressive complaints at all (described in chapter VI). The results of this study were negative. Apparently, the timing of light therapy in the season *per se* is not crucial. However, light treatment at the onset of the syndrome makes it possible to prevent the prevention of the development of severe winter depression.

Final Remarks

Apart from the fact that the studies presented in this thesis provided some opportunities to improve the therapy of winter depression, they also contribute to the scientific debate as to what mechanisms may be responsible for the development of the syndrome and the effects of light. These topics are discussed in the last chapter.

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Chapter II

ASSESSING ATYPICAL SEASONAL AFFECTIVE DISORDER COMPLAINTS BY MEANS OF SELF-RATING

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Summary

The atypical complaints of Seasonal Affective Disorder (SAD) are usually assessed clinically by means of seven questions added to the Hamilton Rating Scale for Depression (HRSDadd). In the present study, these complaints were assessed by means of relevant and modified items of the Beck Depression Inventory (BDIadd), a self-rating instrument. A highly significant correlation between the two assessment procedures was found. This suggest that the BDIadd is a very useful alternative for the HRSDadd.

Introduction

Seasonal Affective Disorder (SAD), winter type, is a depressive syndrome characterized by the occurrence of depression every autumn and winter, followed by complete recovery in spring and summer. In SAD patients, some atypical depressive symptoms are highly characteristic, such as hypersomnia, carbohydrate craving, and weight gain. Fatigue, and loss of social interaction are frequent concomitants (Rosenthal et al., 1984). To some extent, the presence of atypical symptoms has a predictive value for the response to light treatment. Terman et al. reported that the ratio between the atypical symptoms and the total score (including the atypical symptoms) obtained with a depression rating scale was the strongest predictor of the therapeutic response to treatment (Terman et al., 1992).
In the assessment procedures of SAD research, the Hamilton Rating Scale for Depression (HRSD) is the most widely used scale (Hamilton, 1967). When measuring atypical SAD complaints, seven questions are added to the HRSD (HRSDadd) (Rosenthal and Heffernan, 1986), containing items about fatigue, social withdrawal, eating patterns, weight gain and sleep duration.

The HRSD consists of ratings made by a clinician interviewing the patient. The amount of time needed for an accurate HRSD to be completed is considerable (30 minutes or more). The interviewer needs an extensive training to obtain a high interrater reliability, so as to make it possible to compare the scores with those of other clinicians (Post et al., 1985). The use of self-ratings, which requires less time of both clinician and patient, may be an attractive alternative form of assessment. A widely used self-rating instrument for the assessment of depression is the Beck Depression Inventory (BDI)(Beck et al., 1961; 1979; Bouman et al., 1985; Beck and Steer, 1987). Completion of this instrument by the patient only takes 5 minutes and it is a standardized form of measurement, which makes comparisons possible of the results of different (research) centres without the need of special training. An additional advantage of a self-rating instrument is that it facilitates obtaining frequent assessments in longitudinal studies. Such frequent assessments were made by Meesters et al. (1992), who followed the course of depressed mood in SAD subjects over a whole winter season. For that purpose, an addendum to the BDI (BDIadd) was created to assess atypical symptoms of SAD.

In this study, the scores of the HRSDadd and the BDIadd were compared in order to validate the BDIadd for the assessment of atypical symptoms of SAD.

Material and Methods

Data were collected in the winters of 1989-1990, 1990-1991 and 1991-1992. Seventy-six SAD outpatients, all diagnosed according to the criteria of Rosenthal et al. (1984) (20 men, 56 women, mean age 39.0, sd $\pm$ 11.9) each filled out the BDI at 7.30 am. On the same day, the HRSD (17 items) was completed between 9.00 and 11.00 am. The assessment procedures took place before light treatment. The atypical symptoms were measured by the seven questions added to the HRSD (HRSDadd) (Rosenthal and Heffernan, 1986). We created an addendum to the BDI (BDIadd) analogous to the HRSDadd, in order to assess the atypical symptoms by means of self-ratings. This addendum included items 12 (social withdrawal) and 17 (fatigability) from the BDI, as well as items 16 (hypersomnia), 18 (appetite) and 19 (weight gain), which were inversely formulated. The scores for depression on the HRSD and BDI, as well as the scores for atypical SAD symptoms on the HRSDadd and BDIadd were compared by analysis of correlations.

Results

The mean ($\pm$ SD) scores were: BDI: 21.2 $\pm$ 5.5; HRSD: 15.0 $\pm$ 3.7; BDIadd: 5.4 $\pm$ 2.4; HRSDadd: 10.9 $\pm$ 4.9.

Table 1. shows the correlation matrix of items and total scores for the 76 matched HRSDadd and BDIadd ratings. The correlation between BDIadd and HRSDadd scores was highly significant (Pearson: $r = 0.67$, $n = 76$, $p < 0.01$). The matching items for the two scales (the principal diagonal terms) generally showed a higher correlation, ranging from 0.22 to 0.63, than other pairs of items.

A significant correlation was found between the BDI and the HRSD scores (Pearson: $r = 0.45$, $n = 76$, $p < 0.01$).

Table 1. Correlations for pairs of BDIadd and HRSDadd items, for particular BDIadd items and HRSDadd total, and correlations for particular HRSDadd items and BDIadd total

		BDIadd items					BDIadd tot
		fatigue	soc.withd.	hypersomnia	appetite	weight gain	
	fatigue	.22	.01	-.08	-.00	-.16	-.01
	social withdrawal	.14	.28	.02	.23	.01	.21
	hypersomnia	.07	.17	.48	.32	.14	.45
HRSDadd items	appetite increase	.22	.13	.12	.63	.45	.55
	increased eating	.30	.12	.17	.60	.45	.58
	carbohydrate craving	.11	.12	.08	.61	.32	.46
	weight gain	.25	.21	.20	.49	.63	.59
HRSDadd total		.29	.25	.26	.67	.43	.67

Discussion

The scores on the HRSDadd and BDIadd show a higher correlation (r=0.67) than the scores on the original instruments (r=0.45). A possible explanation might be that the contents of the HRSDadd and the BDIadd are quite similar, whereas the original instruments differ to some extent. It should be noted that a relatively low, but still significant, correlation between HRSD and BDI scores is not unusual. Bouman (1987) reported in his thesis a review of studies comparing HRSD and BDI scores. The correlations varied from 0.33 to 0.80. Bailey and Coppen (1976) found a correlation of 0.33 between the scores on the two instruments when obtained on admission. This correlation was higher when patients had been hospitalized for one week or longer. Their explanation of this phenomenon was that, in spite of careful explanation, the questions of the BDI could be confusing when presented to severely depressed patients. The HRSD at admission may be based on incomplete information, due to the fact that the psychiatrist interviews the patient for the first time and has scanty background information (Baily and

Coppen, 1976). When considering our study, with a BDI and HRSD correlation of 0.45, these arguments are only partly valid. Subjects, all outpatients, are already slightly familiar with the BDI, because they have filled it out before (the first assessment being on admission). The manner of administration (self-rating versus clinical rating) may have lowered the correlations. Polaino and Senra (1991) found higher correlations between different depression scales when they were administered in the same way.

Against the background of the above discussion, the relatively high correlation between HRSDadd and BDIadd ($r=0.67$) means that it is possible to assess the atypical symptoms of SAD by means of both instruments in a reasonably valid way. In another study, it was shown that the BDIadd scores could be used to detect the very first signs of a developing winter depression (Meesters et al., 1992). In the absence of an assessment procedure for depression which is undisputedly effective, the most effective strategy is to use multiple measures (Baily and Coppen, 1976; Post et al., 1985; Bouman, 1987). This recommendation applies to SAD research, too. For practical reasons, the BDI together with the BDIadd seems to be a valid instrument for the assessment of SAD in longitudinal studies or when no trained clinicians are available.

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Chapter III

MORNING AND EVENING LIGHT TREATMENT OF SEASONAL AFFECTIVE DISORDER: RESPONSE, RELAPSE, AND PREDICTION

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Summary

Patients with seasonal affective disorder were randomly assigned to treatment with light in the morning (9.00-12.00 am; N=16; ML) or evening (6.00-9.00 pm; N=11; EL). An intensive 24-day assessment procedure revealed the same response rates: 57% for ML, 50% for EL. During the rest of the winter season a relatively low relapse rate of 54% was found. No differences between ML and EL were found in the time course of depressed mood or fatigue. A significant negative correlation was found between diurnal variation during baseline and therapeutic response: the larger the diurnal variation the less the response, indicating a potential negative predictive value for this symptom. There were no significant correlations between baseline fatigue or hypersomnia and response.

Introduction

This report deals with four issues: 1). the importance of the timing of light exposure in the treatment of patients suffering from Seasonal Affective Disorder (SAD); 2). the outcome of light treatment in terms of relapse rates and length of remission; 3). the potential role of fatigue as a mediating variable in the therapeutic process; and 4). the prediction of the therapeutic outcome.

Timing of Light Exposure

An important and still controversial issue in the research of SAD today is the question of whether the timing of light exposure has any significance with respect to its clinical effects. The phase shift hypothesis (Lewy et al., 1987a; Lewy and Sack, 1988b) states that in the majority of patients with SAD the circadian system is phase delayed relative to the timing of the sleep-wake schedule. In a minority of patients the circadian system is phase advanced. These abnormal phase angles may be depressogenic. Exposure to bright light in the morning or evening is thought to be beneficial because it advances or delays the circadian phase. Consequently, in any population of SAD patients, morning light should, generally, be more helpful than light administered at other times of day.
Results of comparisons between exposure in the morning and at other times of day are still inconsistent. Some authors found morning light to be more effective than evening light (Lewy et al., 1987b; Terman et al., 1987; Lewy et al., 1988a; Sack et al., 1990; Avery et al., 1990a; Avery et al., 1990b; Avery et al., 1991). Other studies suggest that the timing of light exposure is irrelevant with respect to the clinical response (James et al., 1985; Hellekson et al., 1986; Wehr et al., 1986; Jacobsen et al., 1987; Terman M. et al., 1989a; Doghramji et al., 1990; Meesters et al., 1990b; Terman J.S. et al., 1990; Wirz-Justice and Anderson, 1990; Wunder, 1990). Rafferty et al. (1990) demonstrated in a statistical meta-analysis that cross-over effects may occur if evening light treatment follows after morning light treatment. Therefore, in the present study patients underwent *one* type of treatment.

Relapse and Remission

Reports on relapse rates vary widely. Some authors report relapses within 3-4 days (Rosenthal et al., 1985a; Rosenthal et al., 1985b; Terman et al., 1989a). In other studies long lasting remission was found (Yerevanian et al.,1986; Wirz-Justice et al.,1986a; Grota et al., 1989; Meesters et al., 1991; 1992a). Wehr et al.(1986) found remissions of intermediate duration, while Wirz-Justice et al. (1986b) reported considerable variability. These discrepancies in relapse rate and length of remission need further investigation. In the present study, these parameters were investigated over long time intervals.

Fatigue

The third issue concerns the relationship between depressed mood and fatigue, particularly with respect to their time courses before, during and after light treatment. Fatigue is, together with hypersomnia, increased appetite, and weight gain, one of the hallmarks of SAD (Rosenthal et al., 1984; Kasper et al., 1989; Terman et al., 1989). However, changes in depressed mood do not always coincide with changes in energy level. Rosenthal et al. (1984) observed that SAD patients felt more energetic and active in spring before their mood improved. Terman et al. (1987), suggested that light might have an "energizing" effect, independent from its effects on mood. Meesters and Lambers (1990a) described a patient with seasonal fatigue, but without any depressive symptoms, who was successfully treated with bright light. Given the evidence of a dissociation of energy loss and depressed mood, it is conceivable that light treatment primarily affects energy levels, and that changes in mood are actually the consequence of changes in energy. In order to explore this possibility, the time relationship between fatigue and depressed mood before, during and after light exposure was studied.

Prediction

The final issue concerns the predictors of treatment outcome. Recently proposed candidates are diurnal variation of mood and "atypical/typical symptom balance".

SAD patients with positive diurnal variations of mood (feeling worst in the morning) have

been reported to show a smaller relapse rate within one week after successful light treatment than patients feeling worst in the evening or those without any diurnal variation of mood (Graw et al., 1991). In the study by Graw et al., the types of diurnal variation were assessed on the basis of the patients' retrospective judgements as given in a diagnostic interview. In the present study, diurnal variations of mood were assessed on the basis of daily morning and evening self-ratings. Parameters derived from these data were studied with respect to their predictive value.

The balance of atypical and typical SAD symptoms was found to be a predictor for the therapeutic response to light treatment (Terman et al., 1992). Patients with relatively more atypical symptoms showed a better response. The symptom balance was evaluated in the present study.

Finally, we address two further issues. Terman et al. (1989a) found that mildly depressed patients responded more favourably than more severe cases, doing so preferentially to morning rather than evening light. We tried to replicate this finding. Additionally, it is unclear whether hypersomnia, as a possible marker of a phase-delayed sleep-wake cycle (Lewy et al., 1987b), is a predictor for preferential response to morning light, or to light per se (Oren et al., 1992). Avery et al. (1991) demonstrated that hypersomnic patients were particularly sensitive to morning light. We analyzed our data with respect to the role of hypersomnia to treatment outcome.

Methods

Subjects and Design

During the winter of 1989-1990, 30 subjects, all outpatients, entered our design for light treatment. All subjects met the criteria for SAD (Rosenthal et al., 1984). The experimental period lasted 24 days: 4 baseline days (this period is called "before"), 5 treatment days ("during") and 15 days after treatment. This last period was split into a 10-day period ("after 1") and a 5-day period ("after 2"). Three subjects dropped out before the end of the light treatment period because of the unpleasant obligation to perform the frequent mood ratings. There were 7 male (mean age 42, sd $\pm$ 10) and 20 female

participants (mean age 45, sd $\pm$ 13). They had all been drug free for at least one month before treatment and stayed so during the whole study.
Admission to the experiment required pre-treatment scores of $\geq$ 13 on the Beck Depression Inventory (BDI; Beck et al., 1961; Beck et al., 1979; Bouman et al., 1985).
The treatment consisted of 3 hours' exposure to bright light on 5 consecutive days. The light fixtures used were 4 full-spectrum fluorescent light tubes (Philips TL 58w/95, in a light box of 66 x 155 cm fixed on the wall, with 2500 lux at an eye-distance of 90 cm, UV light ($<$ 400 nm) was filtered out.
After a randomization procedure, the subjects were assigned to two groups, which were balanced for gender. One group received morning light (ML) from 9.00-12.00 a.m., the other evening light (EL) from 6.00-9.00 p.m. Sixteen subjects received ML, eleven EL.

Assessment Procedures

Depressed mood was assessed three times a day (7.30 a.m., 3.00 p.m., 11.00 p.m.) with the Adjective Mood Scale (AMS; Von Zerssen, 1976 and 1986; Elsenga, 1988) and with a Visual Analogue Scale (VAS-DEP; Albersnagel, 1987). Depression was also assessed on a weekly basis by the Beck Depression Inventory on days 5, 12, 19 and 26 of the experimental period at 7.30 a.m. (BDI; Beck et al., 1961). In addition to these self-ratings, the severity of depression was judged by an experienced psychologist (who was not blind to the treatment conditions) using the 21-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1967). These interviews were conducted before and after treatment (on days 2 and 19 of the experimental period between 9.00 and 11.00 a.m.). In addition, seven supplementary items concerning atypical winter depressive symptoms were assessed (HRSDadd; Rosenthal and Heffernan, 1986a).

Fatigue may be considered one of the constituent components of the multidimensional concept of arousal or activation. Various aspects of activation were assessed in the present study by means of the following self-rating scales:
1. The Activation-Deactivation Adjective Check List (AD-ACL; Thayer, 1976, 1978, and 1986), which measures 4 components of activation: energy, tiredness, tension and calmness.
2. The Stanford Sleepiness Scale (SSS; Hoddes et al., 1973).

3. The Sleep Quality Scale (SQ; Mulder-Hajonides v.d. Meulen et al., 1980).

The AD-ACL and the SSS were completed three times a day during the experimental period of 24 days, together with the AMS (see above); the SQ was filled out daily at 7.30 a.m..

Response and Relapse

Two criteria were used as a definition of a successful response to light treatment. Firstly, the one formulated by Terman et al. (1989a): a score < 8 on the HRSD after treatment, combined with an improvement of at least 50% as compared with the baseline score. Secondly, a response was considered successful if a patient reached a score < 13 on the BDI combined with an improvement of at least 50% on the tenth day after treatment (day 19).

Subjects in whom treatment had been successful according to the HRSD criterion, were considered to have a relapse if a score of at least 13 on the BDI was reached together with a increase on the BDI of at least 100%.

Diurnal Variation of Mood

Various measures of diurnal variation of mood (DV) were distinguished, either on the basis of the actual measurements of daily fluctuations, or retrospectively on the basis of patients' judgements during the HRSD interview.
1) The differences between the morning and evening AMS-scores were calculated for each of the 4 baseline days (7.30 am minus 11.00 pm).
2) The absolute differences between the morning and evening AMS-scores were averaged for the 4 baseline days (henceforth called "mood variability").
3) Diurnal variation was retrospectively assessed by an external rater, before treatment on day 2 of the experimental period. The degree of DV was scored on a 3-point scale, ranging from 0-2 (HRSD, item 18).

On the basis of these measures for DV, groups with and without diurnal variation were

distinguished:

1) Patients with a diurnal variation of mood had a difference in score of at least 6 points on the AMS (see Elsenga & Van den Hoofdakker, 1987) on at least 50% of the baseline days. The remaining patients were considered to have no diurnal variation.

2) Patients having a score of 1 or 2 on item 18 of the HRSD, were considered to be diurnal types (i.e. feeling better in the morning or in the evening), patients having a score of 0, non-diurnal types.

Symptom Balance

The symptom balance was defined as $\frac{\text{HRSDadd-scores}}{\text{(HRSD + HRSDadd)-scores}} \times 100$

(Terman et al., 1992). This is a measure for the relative contribution of atypical SAD symptoms to the total score of severity of depression. In the analysis of the relationship between the symptom balance and the response to treatment, the inclusion criteria of Terman et al. (1992) were used (a baseline score of $\geq$ 20 on the HRSD + HRSDadd, and scores $\geq$ 10 on the HRSD component and $\geq$ 5 on the HRSDadd component). With respect to response definitions we also followed Terman et al. (1992). Responders were those subjects who showed a pre- to post treatment HRSD + HRSDadd score reduction $\geq$ 50%, with subscores of $<$ 8 on the HRSD and HRSDadd. Non-responders showed an improvement of $<$ 30% on the HRSD + HRSDadd, or symptom exacerbation. The remaining subjects were partial responders.

Follow-Up

After the 24-day experimental period, the subjects who had been successfully treated scored the BDI at home on a weekly basis during the remaining part of the winter until April 15th 1990. This period is called the "follow-up period". The subjects whose treatment had been unsuccessful, and those who relapsed during this follow-up period were assigned to the alternative light condition.

Statistics

1) In case of group comparisons, MANOVAs (repeated measures) were applied. Only when interaction effects between time and groups were statistically significant ($p \leq 0.05$), ANOVAs were performed to trace the variables which specifically contributed to these effects. Groups smaller than 5 subjects were not analyzed.
2) Correlations were also calculated. In this way, the disadvantage of artificial cutting points on a continuous dimension could be avoided.

Results

Timing of Light Exposure

Effects of Morning and Evening Light Treatment on Mood and Activation

Table 1. shows the mean scores of the self-rating scales and the HRSD, before, during and after treatment for both treatment conditions. A MANOVA with repeated measures was applied to each variable. For all variables and for each condition a significant main effect was found for the factor time, indicating that a significant improvement occurred in both groups (all p's < 0.05). All MANOVAs were not significant with respect to the interaction between time and group factors. The patients who received ML did not differ statistically from those receiving EL with regard to the various outcome measures.

According to the criterion for full remission, suggested by Terman et al. (1989a; HRSD: -50%, < 8) 57% of the subjects (8 out of 14) in the ML condition and 50% in the EL condition (5 out of 10) were treated successfully. Using the BDI response criterion, 50% of the ML subjects responded (7 out of 14) and 60% of the EL subjects (6 out of 10). In the ML group 1 person who responded according to the HRSD, did not respond according to the BDI of day 19. In the EL group 1 subject responded according to the BDI of day 19, but did not do so according to the HRSD-score.

Table 1. Average scores of 4 time intervals of ML vs EL condition groups

	con	n	before / day 2	during / day12	after1 / day19	after2 / day26
			mean ± sd	mean ± sd	mean ± sd	mean ± sd
HRSD	ML	16	18.1[1] ± 4.8		8.7 ± 6.7	
	EL	11	15.8 ± 2.9		7.1[2] ± 4.9	
HRSD add	ML	16	11.0[1] ± 4.7		5.3 ± 4.8	
	EL	11	13.7 ± 5.7		7.5[2] ± 6.4	
BDI	ML	15	19.5 ± 5.1	14.9[1] ± 8.6	13.1 ± 9.4	11.1 ± 9.9
	EL	10	22.6 ± 3.5	9.6 ± 3.8	12.1 ± 8.1	9.2 ± 8.8
AMS	ML	16	33.0 ± 9.3	24.9 ± 7.5	21.9 ± 9.4	21.1 ± 12.2
	EL	11	39.6 ± 5.5	29.4 ± 14.4	21.1 ± 12.2	20.3 ± 15.6
VAS dep	ML	16	40.6 ± 22.8	34.0 ± 21.7	29.8 ± 22.7	25.5 ± 21.9
	EL	11	41.4 ± 15.0	28.0 ± 20.6	20.7 ± 16.6	15.1 ± 17.7
SSS	ML	16	3.66 ± 0.70	3.24 ± 0.73	3.08 ± 0.88	3.14 ± 0.95
	EL	11	4.14 ± 0.67	3.50 ± 0.90	2.88 ± 0.76	2.98 ± 1.02
SQ	ML	16	1.95 ± 0.78	1.47 ± 0.78	1.27 ± 0.63	1.15 ± 0.80
	EL	11	1.65 ± 0.67	1.55 ± 0.53	1.31 ± 0.55	1.07 ± 0.70
AD-ACL tiredness	ML	16	14.7 ± 2.5	13.1 ± 2.2	12.5 ± 2.1	12.4 ± 2.6
	EL	11	16.5 ± 1.5	14.7 ± 3.0	13.1 ± 2.3	12.8 ± 2.9
AD-ACL energy	ML	16	9.0 ± 2.4	10.9 ± 2.9	11.7 ± 2.7	12.1 ± 2.9
	EL	11	8.2 ± 1.5	10.8 ± 3.4	12.5 ± 2.3	12.8 ± 3.0
AD-ACL calmness	ML	16	13.7 ± 2.1	14.7 ± 1.6	15.1 ± 2.2	15.0 ± 2.2
	EL	11	14.1 ± 2.0	15.0 ± 1.9	15.3 ± 2.0	15.5 ± 2.6
AD-ACL tension	ML	16	11.3 ± 2.4	10.6 ± 2.1	9.8 ± 2.4	9.7 ± 2.6
	EL	11	11.4 ± 1.8	10.0 ± 2.1	9.6 ± 2.4	9.5 ± 2.8

[1] n = 14, [2] n = 10, con = condition, ML = Morning Light, EL = Evening Light. All scores changed significantly over time (MANOVAs; main effect (ML+EL) on time, all p's < 0.05)

Severity of Depression

Terman et al. (1989a) reported that the therapeutic response of mildly depressed subjects (HRSD-scores $\leq$ 16) was superior to that of more severely depressed subjects. In the current study, patients were subdivided on the basis of the same criteria: the "mildly depressed": HRSD $\leq$ 16, n = 11, and the "severely depressed": HRSD > 16; n = 16. Table 2. shows the HRSD-scores of both groups and the treatments they received.

Table 2. Average scores of the HRSD of the mild vs severe SAD groups

MILD versus SEVERE	con	n	HRSD BEFORE mean ± sd	HRSD AFTER 1 mean ± sd
HRSD > 16	ML	8	21.4 ± 3.6	10.9 ± 7.6
	EL	6	17.8 ± 1.5	6.2 ± 4.8
	TOT	14	19.9 ± 3.3	8.9 ± 6.8
HRSD ≤ 16	ML	6	13.7 ± 1.0	6.2 ± 6.1
	EL	5	13.4 ± 2.3	8.5[1] ± 5.4
	TOT	11	13.5 ± 1.6	7.1[2] ± 5.6

[1] n = 4, [2] n = 10, con = condition, TOT = ML + EL. See text for other abbreviations.

Neither MANOVA of the total group (ML and EL together), nor analysis of the ML group separately, showed significant interaction effects between the severity factor and the time factor. The number of subjects in the EL condition was too small for analysis.

A correlational approach (ML and EL together), however, resulted in a significant positive correlation between the baseline severity of depression and the response to treatment (delta values of the two HRSD-scores)(Pearson: r = 0.54, n = 24, p = 0.01; Spearman: r = 0.52, n = 24, p = 0.01).

Chapter III

Hypersomnia

In the study by Avery et al. (1991), patients were subdivided into two groups, those reporting complaints of hypersomnia, i.e., a sleep duration of at least 1 hour longer than usual as reported on the baseline HRSDadd, and those reporting no complaints. We made the same distinction in our sample. Table 3. shows the data.

Table 3. Average scores of the HRSD of SAD patients with and without hypersomnia

	con	n	HRSD BEFORE mean ± sd	HRSD AFTER 1 mean ± sd
WITH HYPER SOMNIA	ML	7	17.9 ± 4.9	10.0 ± 6.4
	EL	9	15.4 ± 2.3	6.9[1] ± 5.3
	TOT	16	16.5 ± 3.9	8.3[2] ± 5.8
WITHOUT HYPER SOMNIA	ML	7	18.3 ± 5.1	7.7 ± 8.2
	EL	2	17.5 ± 3.5	8.0 ± 4.2
	TOT	9	18.1 ± 4.6	7.8 ± 7.3

[1] n = 8, [2] n = 15, con = condition, TOT = ML + EL. See text for other abbreviations.

No significant interaction effect was found between the total group (ML+EL, with/without hypersomnia) and time (before/after treatment). Similarly, no significant interaction effect was found between the ML group (with/without hypersomnia) and time. The number of subjects in the EL condition was too small for analysis.

Comparison of the courses of depression in the two treatment conditions of the hypersomnic patients (ML: n = 7 and EL: n = 8) yielded no significant interaction effect between condition and time.

Relapse and Remission

Eleven subjects (6 receiving ML and 5 EL) did not show a complete recovery in response to light treatment (HRSD: -50%, $<$ 8). If subjects scored $\geq$ 13 on the BDI on the last day of our experimental period (day 26), they were offered a second light treatment in the other condition. Nine subjects were actually given this alternative treatment (ML: 4, EL: 5). After this second treatment, 5 subjects responded favourably (ML: 2 and EL: 3).
Of the 13 subjects who were treated successfully (HRSD-criterion), 7 relapsed during the same winter (54%), two of them within two weeks after light treatment, another 2 in the third week, the remaining three subjects in week 8, 12 and 14 respectively. Six subjects (46%) did not relapse at all (the experiment ended on 15 April); two of them had been monitored for 9 weeks, one 12 weeks, one 16 weeks and two 21 weeks after light treatment. Using the BDI response criterion, 10 out of 17 subjects (59%) relapsed, whereas 7 subjects (41%) did not relapse at all during the same winter.

Fatigue

The course of mood and fatigue, and the effects of light

To study possible differences in the time courses of depression and fatigue scores, the average daily scores of the VAS-DEP were compared to the average daily AD-ACL-tiredness subscale. For that purpose, the scores were normalized on a scale of 0-100. Fig. 1. shows the average daily normalized scores of tiredness and depression for the two treatment conditions (Fig. 1a ML and Fig. 1b EL).
The difference in the time courses of mood and tiredness between patients treated with ML and EL, was examined over two periods of time. Over the entire experimental period (24 days), no significant interaction effect was found between conditions (ML/EL), self-rated variables (tiredness/depressed mood) and time. Nor was any interaction effect found between tiredness and depressed mood on the one hand and time on the other, when EL and ML groups were pooled. Furthermore, when a shorter period of time was chosen, viz., the 2 baseline days before the first light pulse and 3 subsequent treatment days, no significant interaction effect was found between conditions (ML/EL), self-rated variables (tiredness/depressed mood) and time. Similarly, no significant difference was found

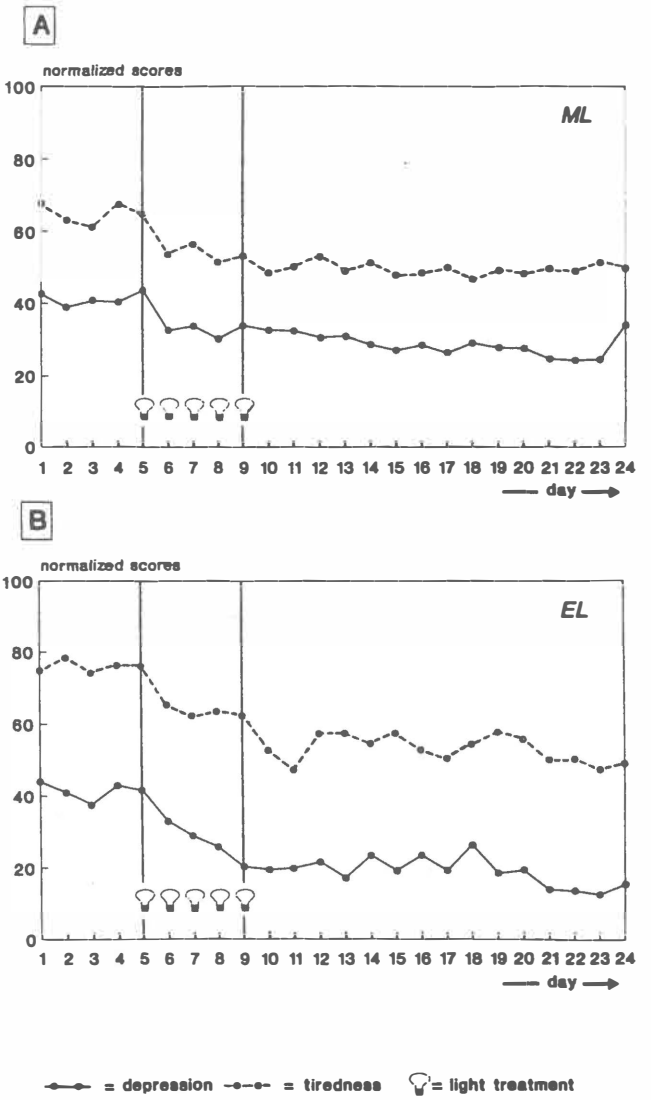

Fig. 1. The course of depression and tiredness during the 24 day experimental period. The ranges of the Activation-Deactivation Adjective Check List (AD-ACL)-tiredness subscale (tiredness) and the Visual Analogue Scale for Depression (depression) are normalized from 0-100 (high score = severe complaints). ML = morning light treatment (9.00-12.00 a.m.; n = 16); EL = evening light treatment (6.00-9.00 p.m.; n = 11). The scores are the average daily scores based on assessments at 7.30 a.m., and 3.00 and 11.00 p.m.. No significant differences between the courses of mood and fatigue were found.

between the course of tiredness and depressed mood when EL and ML groups were pooled. Hence, we were not able to find any evidence that changes in fatigue after light treatment precede changes in mood.

Baseline Fatigue

In Table 4. two groups are presented, one with a low, the other with a high level of fatigue, i.e., with average baseline scores in the lowest and highest quartiles of the AD-ACL-tiredness scores, respectively. The HRSD-scores were corrected by removing the scores on the two questions about complaints of fatigue (items 7 and 13). MANOVA of the pooled ML and EL data revealed no significant interaction effect between group (low/high fatigue) and time. Although this interaction effect was not significant, it is worth mentioning that the severely fatigued group showed a significant improvement on the corrected HRSD ($F(1,6)$: 30.86; $p = 0.00$), whereas the non-fatigued group did not ($F(1,5)$: 1.00; $p = 0.36$).

As a second approach to the potentially predictive value of fatigue to treatment response, correlations were calculated between the average baseline levels of tiredness (AD-ACL), sleepiness (SSS) and sleep quality (SQ) on the one hand, and the HRSD (minus items 7 and 13) response to light treatment on the other. A significant correlation was found between tiredness and response to treatment (Pearson: $r = 0.46$; $n = 24$, $p = 0.03$), and a trend between sleepiness and response to treatment (Pearson: $r = 0.40$; $n = 24$, $p = 0.05$). The correlation between sleep quality and response to treatment is not significant. Non-parametric rank correlations (Spearman) did not reveal significant relationships.

Table 4. Average HRSD scores of SAD patients with more or fewer complaints of fatigue

	con	n	HRSD BEFORE mean ± sd	HRSD AFTER 1 mean ± sd
AD-ACL tired highest quartile	ML	2	11.5 ± 4.9	1.5 ± 2.1
	EL	5	12.0 ± 1.9	4.4 ± 1.1
	TOT	7	11.9 ± 2.5	3.6 ± 1.9
AD-ACL tired lowest quartile	ML	6	12.4[1] ± 2.1	7.7 ± 6.2
	EL	1	8.0	13.0
	TOT	7	11.6 ± 2.4	8.4 ± 6.0

[1] n = 5, con = condition, TOT = ML + EL. HRSD-scores without item 7 & 13. See text for other abbreviations.

Prediction

Diurnal Variation of Mood

Diurnal Variations as measured by Daily Self-Ratings

Subjects were divided into two groups: those with and those without DV's (see methods section). Table 5. shows the responses to treatment of these groups.

A significant interaction effect between group and time was found ($F(1,22)$: 6.60; $p = 0.02$), indicating that the course of depression differed for the two groups. Patients without DV's were more depressed than patients with DV's ($F(1,22)$: 6.80; $p = 0.02$). Both groups showed a significant decrease of depression (non-DV: $F(1,22)$: 41,40; $p = 0.00$ and DV: $F(1,22)$: 13.10; $p = 0.00$), but did not differ in degree of depression after treatment ($F(1,22)$: 1.15; $p = 0.30$). Hence, the interaction effect between group and time may partly be explained by differences in baseline depression. It should be remembered that the severity of baseline depression was positively correlated to response.

Table 5. Average HRSD scores of SAD patients with and without diurnal variation of mood

	con	n	HRSD BEFORE mean ± sd	HRSD AFTER 1 mean ± sd
with diurnal variation (AMS)	ML	12	14.9[1] ± 3.1	8.5 ± 6.9
	EL	5	13.6 ± 2.5	8.3[2] ± 6.4
	TOT	16	14.5[3] ± 2.9	8.4 ± 6.5
without diurnal variation (AMS)	ML	4	21.3 ± 6.5	6.5 ± 3.4
	EL	6	17.0 ± 2.3	5.8 ± 3.3
	TOT	10	18.7 ± 4.7	6.1 ± 3.1
with diurnal variation (HRSD)	ML	11	16.7 ± 5.0	9.0 ± 6.8
	EL	3	15.3 ± 3.5	5.5[4] ± 6.4
	TOT	14	16.4 ± 4.6	8.5[5] ± 6.6
without diurnal variation (HRSD)	ML	3	16.7 ± 6.4	5.0 ± 5.3
	EL	8	15.5 ± 2.9	7.1 ± 4.5
	TOT	11	15.8 ± 3.8	6.5 ± 4.6

[1] n = 10, [2] n = 4, [3] n = 15, [4] n = 2, [5] n = 13, HRSD-scores without item 18, con = condition, TOT = ML + EL. See text for other abbreviations.

Diurnal Variation as assessed by HRSD

The global assessment of diurnal variation was obtained in the HRSD interview before treatment. Patients reported only positive DV's (feeling worst in the morning), or no DV's. No significant interaction effect was found between the factors group (DV-HRSD and non-DV-HRSD) and time.

Variability of Mood as measured by Daily Self-Ratings

As a third approach, the relation between the variability of mood (the average of the absolute differences of AMS morning and evening scores on the 4 baseline days) and the treatment outcome (the difference between HRSD-scores before and after treatment, both minus the score on item 18) was investigated. It was found that the less variability patients showed before treatment, the more favourably they responded to light treatment (ML and EL taken together: Pearson: $r = -0.46$, $n = 24$, $p = 0{,}02$ and Spearman: $r = -0.47$, $n = 24$, $p = 0.02$).

Symptom Balance

For the calculation of the symptom balance, twenty-one subjects met the inclusion criteria as defined by Terman et al. (1992). Eleven responded, 6 did not and 4 only partially. Contrary to our expectations, correlations of symptom balance and response showed a negative trend (Pearson: $r = -0.43$, $n = 21$, $p = 0.051$): a larger contribution of atypical SAD symptoms to the total score of depression (HRSD + HRSDadd) tended to lead to a less favourable response to light treatment (the differences in scores of the HRSD before and after treatment). The symptom balance did not correlate significantly with the HRSD + HRSDadd improvement, nor with the HRSDadd improvement.

Discussion

Phase shift

The question of whether the responses of SAD patients to ML differ from those to EL, is central to the phase shift hypothesis posed by Lewy et al. (1987a; 1988a). Although we did not "phase-type" the patients in this study, we found no support for this hypothesis. Based on the observation that delay-type patients are more common than advance type patients (Lewy et al., 1988a) patients receiving ML should show, on average, a better response than those receiving EL. In our study, no differences in response to ML and EL were found (57% versus 50%). This contradicts the results from a meta analysis by Terman et al (1989a), which showed a significant difference (53% versus 38%). This discrepancy may be due to ordering effects in some of the studies included by Terman et al. (Rafferty et al.,

1990). Terman et al. (1989a) did not control for these rank order effects.

Terman et al. (1989a) and Stinson and Thompson (1990) reported that patients with relatively low baseline depression scores were more responsive to light, especially when applied in the morning. We were not able to replicate these findings. In our study, there was a positive correlation between baseline severity and response, although this finding may be artificial because the measure of response partly overlaps with the baseline measure. A positive correlation between baseline severity and treatment response has also been reported for the response to sleep deprivation (Kuhs & Tölle, 1991). Inspection of the data does not suggest a different response to ML and EL in mildly depressed patients.

Hypersomnia was found to be related with a favourable response to light treatment in a study of Oren et al. (1992). Their results were based on the pooled data from 5 studies, using light of different wavelengths, with only female, outpatient subjects, and flexible individual time schedules for the light treatment (1 week for 2-6 hours per day). In our study, the data are based on one light regime (same wavelength and duration) in a sample of both sexes. We did not find such a relationship.
Avery et al. (1991) found that patients with complaints of hypersomnia showed a better response to ML. If hypersomnia were to be the result of a phase delay of the circadian system relative to the sleep wake cycle, their findings would support the phase shift hypothesis. The data in the present study, however, are at variance with the findings of Avery et al. (1991). Perhaps this is due to the relatively late application of morning light in the present study (9.00 a.m. versus 6.00 a.m. in Avery et al.). On the other hand, our results are in line with a study of Wirz-Justice and Anderson (1990), who found no evidence that SAD patients with hypersomnia respond differently to ML and EL.

Although no support was found for the phase shift hypothesis, some critical comments must be made. Our ML was administered late in the morning and our EL early in the evening. ML administered at an earlier time of day might have resulted in better responses. This explanation is not very likely though, since our ML response percentages are in line with those obtained by others who used time schedules between 5.30 and 8.00 a.m. (Terman et al., 1989a). Furthermore, we did not control for outdoor light exposure. In order to explain the similar effects of ML and EL through differences in outdoor light

conditions, it has to be assumed that, during the treatment period, the EL group was exposed to outdoor light for a longer time than during the baseline period. This is not very likely either. A further point is, that we did not control for the effects of sleep deprivation. Some subjects had to wake up earlier and go to bed later than usual because of the design (assessment times at 7.30 a.m. and 11.00 p.m.). The accompanying sleep deprivation effects will not have differed for the two groups in the baseline period. However, in the treatment period and after, this may have been different, especially if light treatment had shifted the preferred timing of sleep. Possible energizing effects of light (Lewy et al., 1988) could also have differentially influenced sleep latency. Hence, the possibility of differential sleep curtailment cannot be excluded.

Relapse

According to the literature, most SAD patients relapse, doing so on average within 3-4 days after light treatment (Terman et al., 1989a). The relapse rate in our study, during the remaining part of the winter after treatment, is relatively small (54%). The timing of the treatment relative to the onset of depression may play a role in the percentage and timing of relapses. It has been demonstrated that relapse can be prevented during the remaining winter season when treatment is administered at the very first stage of depression onset (Meesters et al., 1991; 1992a). Hence, discrepancies between studies with respect to outcome may be partially explained by differences in the interval between the onset of the illness and the start of the treatment.

Fatigue

Decrease of fatigue did not precede improvement of the affective symptoms. Scores on depression and tiredness scales ran a parallel course before, during and after light treatment. However, tiredness possibly plays a role in the prediction of the response to treatment: a trend was found that the more tired and sleepy patients were, the better they responded to light treatment. Young et al. (1991) found that fatigue was among the most prominent complaints at the time the illness started to develop. Hence tiredness remains an intriguing aspect of SAD.

Prediction

SAD may be accompanied by diurnal changes of mood. The few studies on the importance of this phenomenon to the response to light are based on patients' retrospective judgements. Graw et al. (1991) observed a positive relationship between the presence of diurnal variations and treatment outcome. However, retrospective assessment of diurnal variations may be problematic (Stieglitz et al., 1988). Diurnal variation of mood is considered an important symptom of non-seasonal major depression (Nelson and Charney, 1981). Diurnal variations and mood variability, assessed on a daily basis, have indeed been shown to have a strong predictive value with respect to treatment outcome in non-seasonal major depression: the more diurnal variations of mood occur the more patients benefit from specific treatments. Positive correlations have been found between the degree of diurnal variation and mood variability on the one hand, and the response to sleep deprivation on the other (Reinink et al., 1990 and 1992; Haug, 1992). The response to a tricyclic antidepressant has also been shown to be positively correlated with diurnal variation (Haug and Stieglitz, 1990).
We found the opposite results in SAD patients: more diurnal variations and a larger variability in mood were related with less favourable treatment outcome. This may be one more feature pointing to a fundamental difference between seasonal and non-seasonal affective disorder, apart from differences in sleep, appetite, and responsiveness to light (Yerevanian et al., 1986). This suggestion seems to be complemented by the results of Terman et al. (1992), who found that a relatively large contribution of atypical SAD symptoms to the depression was the "strongest predictor" of treatment response. This finding was not confirmed in the present study. Actually, a trend in the opposite direction was found. We have no specific explanation for this discrepancy. Differences in group size and severity of clinical state may be responsible.

Finally, we would like to make some comments on some general issues in this area of research. As demonstrated in the former paragraphs, the numerous studies in this field have provided a large variety of results: differences in response rates, relapse rates, response prediction, etc. This variety may be due to differences in group sizes, treatment variables and outcome measures. However in view of the small number of patients in many of the studies, it is conceivable that differences in results reflect differences in patient

characteristics. One such characteristic might be susceptibility to the placebo component of the treatment (Eastman, 1990). In this context an experiment by Richter et al. (1992) is worth mentioning. They compared two treatments. One group of patients was treated with hypnosis. During the hypnotic sessions, the patients were made to imagine that they perceived bright light. The other group was treated with real light. Immediately after treatment both groups showed the same improvement. One week after treatment, the effects of the imaginary light had disappeared. The experiment demonstrates that "suggestibility" might be an important determinant of response. This may not be the only important personality trait. SAD patients have been found to have personality profiles which differ from those of healthy controls (Meesters, 1992b). In our opinion, personality variables should receive much more attention in future research.

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Chapter IV

10,000 LUX BRIGHT LIGHT THERAPY FOR SEASONAL AFFECTIVE DISORDER IN VARIOUS TEMPORAL SCHEMES

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Summary

68 patients with seasonal affective disorder participated in a 10,000 lux light treatment study in which three questions were addressed.

A. Do response rates differ when the light is applied at different times of the day? In order to answer this question three groups of patients received a four day light treatment (I) either in the morning (8.00-8.30 a.m., n=14), or (II) in the afternoon (1.00-1.30 p.m., n=15) or (III) in the evening (8.00-8.30 p.m., n=12) . Response rates amounted to 69, 57 and 80% respectively, the absence of significant differences indicating that the timing of the light is not critical.

B. Does short term rank ordering of morning and evening light influence response rates? To answer this question, two additional groups of patients received two days of morning light treatment, followed by two days of evening light (IV, n=13) or vice versa (V, n=14). Response rates were 67 and 50% respectively. This difference was not statistically significant, nor did the percentages differ significantly from those of group I and III, indicating that short term ranking of morning and evening light does not influence therapeutic outcome.

C. Do the 5 treatment modes cause different relapse rates? The number of patients who relapsed after successful treatment were 3/8, 2/8, 3/7, 0/8, and 0/7 respectively. There were no statistically significant differences. An overall low relapse rate of 21% was found.

Introduction

Seasonal Affective Disorder (SAD), winter type, is a depressive syndrome appearing almost every year in the autumn/winter (Rosenthal et al., 1984). Exposure to light has been shown to be an effective treatment (Terman et al., 1989). Whether or not the timing of light treatment is a critical factor is still controversial (Blehar and Lewy, 1990; Wirz-Justice and Andersen, 1990). This report deals with several aspects of this issue. Firstly, the importance of timing *per se* is addressed. Secondly, the influence of the rank order of light exposure is studied. The third topic concerns the relation between the timing of treatment and relapse.

Timing

In an attempt to explain the occurrence of SAD and the therapeutic effects of light, it has been hypothesised that SAD patients suffer from an abnormality in the phase relation between the circadian system and the sleep wake cycle (Lewy et al., 1987a). According to this hypothesis, the circadian system in the majority of SAD patients is thought to be phase delayed with respect to the sleep wake cycle, in a minority of patients phase advanced. These abnormal phase angles are considered to be depressogenic, with the assumption being that light treatment would normalize these phase abnormalities. Therefore, in the majority of SAD patients bright light in the morning is thought to be beneficial, because it advances the circadian phase. In contrast, in the phase advanced SAD patients, evening light would be therapeutic through its phase delaying effects (Lewy et al. 1985, 1987a, 1988a; Lewy and Sack,1988b). Empirical research has provided contradictory results. Some authors have reported morning light to be more effective than evening light (Lewy et al., 1987b, 1988a; Terman et al., 1987; Avery et al., 1990a, 1990b, 1991; Sack et al 1990; Terman et al., 1990a), while others have found that the timing of light exposure was not a critical factor for a clinical outcome. There are even indications that light in the middle of the day may be effective (James et al., 1985; Hellekson et al., 1986; Wehr et al., 1986; Wirz-Justice et al., 1986a, 1993; Yerevanian et al., 1986; Jacobsen et al 1987; Isaacs et al., 1988; Terman et al 1989; Doghramji et al., 1990; Meesters et al., 1990, 1993a; Wirz-Justice and Anderson, 1990; Wunder, 1990).

Some authors have attributed the contradictory results of the various studies to differences in patient characteristics. Whereas patients with hypersomnia would preferably respond to morning light, patients with insomnia were thought to respond to morning light and evening light to the same degree (Lam, 1992). Others have noted a dependence of baseline depression severity (Terman et al., 1989; Stinson and Thompson, 1990) and of daily mood fluctuations in the baseline period (Meesters et al., 1993a). In the present study, the effects of light in the morning, afternoon and evening are compared and possible predictors of the responses examined.

Rank Order

Because of differences in designs and methods used, the studies on the timing of light exposure are only comparable to a limited extent. In most studies, a cross-over design was used, the assumption being that subjects who have been treated successfully, will relapse within 2-4 days in the withdrawal period (Rosenthal et al., 1985a, 1985b; Wehr et al., 1987; Terman et al., 1989). A disadvantage of this type of design is the possible induction of rank order effects (Blehar and Lewy, 1989). In a retrospective statistical meta-analysis of existing studies Rafferty et al. (1990) found evidence that morning light, when given as the first treatment, could render subsequent evening light ineffective. In contrast, evening light when given as the first treatment, would be equally effective as morning light when given as the initial treatment, which suggests that evening light does not block the effects of subsequent exposure to morning light. Some clinical data from a more recent study by the same authors would seem to support this possibility (Terman, et al., 1990a).
A change in retinal sensitivity, resulting from morning light, has been hypothesized as a possible mechanism of this carry-over effect (Rafferty et. al. 1990; Remé et al., 1990). In this view, both morning light and evening light, when given as the first treatment, are equally effective in inducing a therapeutic response. Due to some unknown adaptation process (possibly linked to visual sensitivity and/or rod disk shedding which peak in the early morning), the sensitivity threshold for light pulses would increase after morning light, but not after evening light. If evening light is administered as the second treatment, the desensitizing effect of morning light would make evening light less effective. However, if evening light treatment follows on evening light, this second evening light treatment still elicits in a response.

A response to light treatment usually occurs within 3-4 days (Terman et al., 1989). Therefore, in order to examine the effects of ranking evening and morning light, we chose a design in which groups of patients were exposed to two days of evening light treatment followed by two days of morning light treatment, and vice versa. Thus we avoided a complete recovery in subjects who had just received the first treatment modality. The second modality then had the opportunity to positively contribute to the recovery. If morning light has the more powerful effect on the daily photoreceptor renewal processes (which would be disturbed in SAD patients according to Remé et al., 1990), morning light in the early days of treatment should reduce the effectiveness of subsequent evening light. The response to evening light followed by morning light, in contrast, would not be influenced by the first condition. Therefore, a better response was expected in the condition with evening light as the first treatment.

This approach has some additional advantages. Comparing the effects of different rank orders of treatment in this design is less sensitive to misinterpretations due to placebo effects than in a cross-over design (Terman et al., 1990a). A cross-over design makes use of the relapse after the first treatment modality has ended. Relapse is a highly variable phenomenon in terms of timing, degree and rate. The present design avoids the influence these sources of variability have on the outcome of treatment.

Relapse

Reports on relapse vary widely. Some authors report relapses within 2-4 days (Rosenthal et al., 1985a, 1985b; Wehr et al., 1987; Terman et al., 1989). Others have not found such rapid relapses (Wehr et al., 1986; Wirz-Justice et al., 1986a; Yerevanian et al., 1986; Grota et al., 1989). According to Wirz-Justice et al. (1986b), the time interval between treatment response and relapse shows extreme variation. They found that some patients relapsed within 1 day after treatment, while others remained free of symptoms for the rest of the winter season. Terman et al. (1990a) found a relapse rate of 86% within two weeks of withdrawal, while Meesters et al. (1993a) observed that 46% of those improved stayed well throughout the entire winter season (an average period of 14.7 weeks). The majority of Lingjaerde et al.'s patients (1993) experienced the beneficial effects of light treatment for the rest of the season or at least for several weeks after having received light treatment for one week. It must be inferred that relapse is a highly variable phenomenon across

studies.
Since the occurrence of relapses is both crucial in cross-over studies and has major clinical significance, in the present study, patient assessments were made during the rest of the winter season. One of the questions dealt with is that of whether the various temporal schemes influence the relapse rate.

To sum up, in the present study three questions are addressed. The first question concerns the clinical effectiveness of light treatment as a function of the time of administration: Are there differences in response to light applied in the morning, the afternoon, or the evening? What patient characteristics predict response?
Secondly, the question is raised whether short term rank ordering of morning and evening light treatment influences the therapeutic results in SAD patients. For this purpose, two additional groups were studied. Each treatment consisted of either two days of evening light and two days of morning light, and vice versa.
Finally, the third question dealt with the variance in relapse rate. To what extent does the variance in relapse rate relate to the temporal scheme of light application?

Methods

Subjects and Design

During the winters of 1990-1991, 1991-1992 and 1992-1993, a total of 82 outpatients entered the design of the study. All subjects both met the criteria for SAD by Rosenthal et al. (1984), and those for seasonal pattern according to the DSM-III-R (APA, 1987; Koster van Groos, 1988). All patients had been drug free for at least three weeks before light treatment and remained so during the experimental period. Patients were, balanced for gender, randomly assigned to one of the five following conditions (see Fig. 1.):
1. C1: two days of morning light (8.00-8.30 a.m.) followed by two days of evening light (8.00-8.30 p.m.).
2. C2: two days of evening light followed by a day without treatment and two days with morning light. The intervening day without light leads to 36 hours between treatments, as in condition C1.
3. C3: four days of morning light

4. C4: four days of evening light
5. C5: four days of light treatment in the afternoon (1.00-1.30 p.m.).

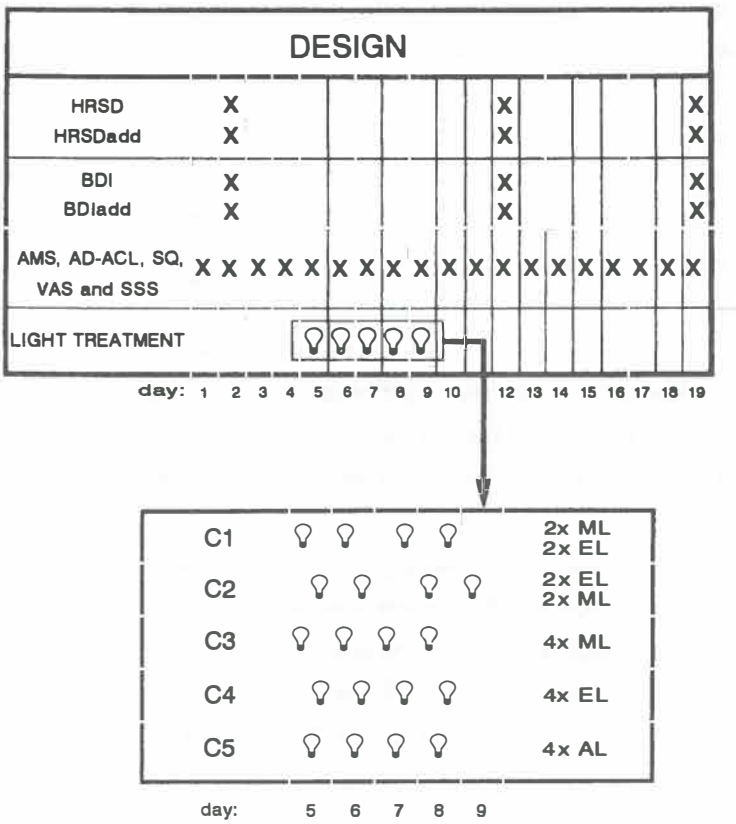

Fig. 1. The experimental design. Light bulbs indicate treatment days. ML = Morning Light (8.00-8.30 a.m.); EL = Evening Light (8.00-8.30 p.m.), AL = Afternoon Light (1.00-1.30 p.m.). See text for other abbreviations.

Each subject only participated in a single condition of the design. They had to visit the clinic for light treatment. The subjects were asked to avoid bright indoor and outdoor light during the time intervals in which the other subjects received light treatment.
The experimental period lasted 19 days: 4 baseline days, 4 (5) treatment days, and 11 (10) days after treatment. [1]

Admission to the experiment required pre-treatment scores of at least 13 on the Beck Depression Inventory (BDI; Beck et al., 1961, 1979; Bouman et al., 1985; Beck and Steer, 1987). If subjects had a BDI score <13 on day 5 (just before light treatment), they were excluded from analysis. This happened to 8 subjects. After successful treatment, subjects filled out the BDI and BDIadd at home (Meesters and Jansen, 1993c) on a weekly basis and mailed their scores to the clinic. In case of relapse, subjects were offered a second or, if necessary, more light treatments.
Since 30 minutes of 10,000 lux light application have been shown to be very effective (Terman et al., 1990a; Magnusson and Kristbjarnarson, 1991; Arbisi et al., 1993; Rosenthal et al., 1993; Terman and Terman 1993), and since no ophthalmological problems were reported after this high light intensity (Gallin et al., 1990, Terman et al., 1990b), we chose a four day 10,000 lux treatment of 30 minutes. The light fixtures used (Ultra Bright 10,000, UB Medic Light, Inc) were identical to those described by Terman et al. (1990a).
Thirteen subjects had received light therapy in a previous winter season, the other 55 subjects received light treatment for the first time in their lives.
Six subjects did not complete the design, mainly because of the unpleasant obligation of having to perform frequent mood ratings. 68 subjects participated in the analyses, 16 men (mean age 38.0 $\pm$ 10.6), 52 women (mean age 37.1 $\pm$ 10.4).

Assessment Procedures

Depressed mood was assessed three times a day (7.45 a.m., 7.45 p.m., 10.45 p.m.) by means of the Adjective Mood Scale (AMS; Von Zerssen, 1976, 1986; Elsenga, 1988), and a Visual Analogue Scale (VAS-DEP; Albersnagel, 1987). Depression was also assessed on

[1] The numbers in brackets refer to condition C2

a weekly basis by the Beck Depression Inventory, 21 items version, on days 2, 5, 12, and 19 of the experimental period at 7.45 a.m. (BDI; Beck et al., 1961; 1979; 1987). In addition, the severity of depression was judged by an experienced psychologist (not blind to the treatment conditions) using the 21-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1967). These interviews were conducted once before and twice after treatment (on days 2, 12 and 19 of the experimental period between 9.00 and 11.00 a.m.) at the clinic. In addition, seven supplementary items concerning atypical winter depressive symptoms were assessed (HRSDadd; Rosenthal and Heffernan, 1986a). The atypical complaints were also assessed by means of an addendum to the BDI (BDIadd; Meesters and Jansen, 1993c; Meesters et al. 1994).

Fatigue may be considered one of the constituent components of the multidimensional concept of arousal or activation. Various aspects of activation were assessed in the present study by means of the following self-rating scales:

1. The Activation-Deactivation Adjective Check List (AD-ACL; Thayer, 1976, 1978, and 1986), which measures 4 components of activation: energy, tiredness, tension and calmness.
2. The Stanford Sleepiness Scale (SSS; Hoddes et al., 1973).
3. The Sleep Quality Scale (SQ; Mulder-Hajonides v.d. Meulen et al., 1980).

The AD-ACL and the SSS were completed three times a day during the experimental period of 19 days, together with the AMS (see above); the SQ was completed on a daily basis at 7.45 a.m..

Diurnal Variation of Mood

Diurnal variation of mood was defined as the average of the absolute differences between the morning and evening AMS-scores during the 4 baseline days (7.45 a.m. minus 10.45 p.m). Thus defined, diurnal variation has been shown to have a predictive value for treatment outcome (Meesters et al., 1993a).

Response and Relapse

Patients were considered to respond if their final HRSD-score on day 19 had dropped

below 8, with a maximum of 50% of the baseline score (Terman et al., 1989). Subjects who had responded, were considered to have relapsed if their score on the BDI had reached 13 or over and if this score represented an increase of at least 100% .

Statistics

In case of group comparisons, MANOVAs (repeated measures) were applied. Only when interaction effects between time and groups were statistically significant ($p \leq 0.05$), ANOVAs were performed to trace the variables which specifically contributed to these effects. In addition, correlations were calculated to avoid the disadvantage of artificial cutting points.

Results

The mean scores of the BDI, BDIadd, HRSD and HRSDadd at the various points of time for each of the five conditions are shown in Table 1. This table also presents the ratios between post-treatment and pre-treatment scores.

According to the HRSD response criterion (< 8 and improvement of at least 50%), the response figures, assessed on the 10th day after light treatment, are 67, 50, 69, 80 and 57% respectively for the five conditions. The groups did not differ with respect to gender or age. Subjects with and without experience of light therapy turned out to be equally distributed over the groups.

The individual scores on the other self-rating scales were averaged per day. For each condition, these individual average daily scores were averaged in turn. The resulting mean daily scores per condition are presented in Table 2. (see also Fig. 2.).

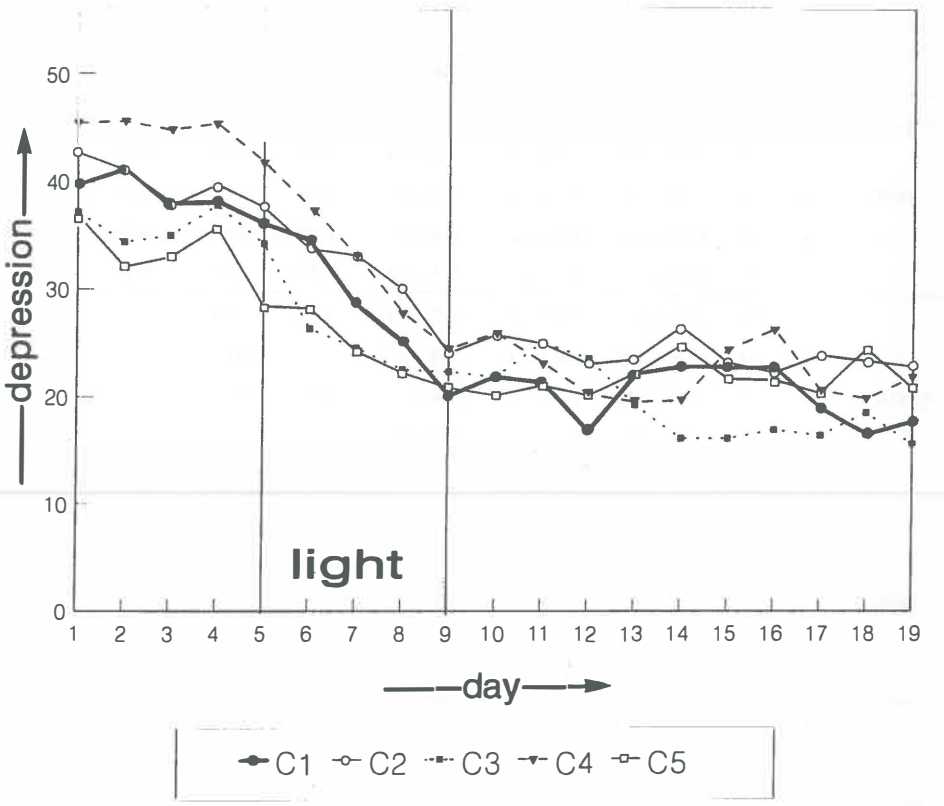

Fig. 2. The course of depressed mood (Adjective Mood Scale) during the experimental period. C1 = Morning Light/Evening Light, C2 = Evening Light/Morning Light, C3 = Morning Light (8.00-8.30 a.m.), C4 = Evening Light (8.00-8.30 p.m.), C5 = Afternoon Light (1.00-1.30 p.m.). The figure represents the mean daily scores for each condition.

Table 1. Average scores on the BDI and HRSD of 3 time intervals of 5 treatment condition groups

	con	N	mean ± sd day2	mean ± sd day 12	mean ± sd day 19	ratio d12/d2	ratio d19/d2	<8,-50% d12	<8,-50% d19
	1	13	19.0 ± 3.8	10.0 ± 6.0	6.5 ± 5.9[3]	0.54	0.33	0.38	0.67
	2	14	16.2 ± 4.0	9.1 ± 7.7	8.2 ± 7.8	0.57	0.51	0.36	0.50
HRSD	3	14	16.9 ± 3.8	7.7 ± 6.4[3]	4.7 ± 4.0[4]	0.45	0.28	0.50	0.69
	4	12	17.5 ± 1.1	8.0 ± 6.2[2]	5.5 ± 3.7[1]	0.45	0.32	0.55	0.80
	5	15	15.9 ± 3.4	9.1 ± 4.6	8.4 ± 5.7[5]	0.57	0.51	0.40	0.57
	1	13	9.1 ± 4.4	4.0 ± 2.1	3.7 ± 3.1[3]	0.54	0.43		
	2	14	10.6 ± 4.7	6.6 ± 6.4	6.4 ± 6.9	0.67	0.63		
HRSDadd	3	14	9.9 ± 5.5	4.9 ± 3.6[3]	3.4 ± 3.9[4]	0.55	0.37		
	4	12	10.6 ± 2.4	5.5 ± 3.6[2]	4.4 ± 3.8[1]	0.49	0.43		
	5	15	12.0 ± 4.1	6.7 ± 3.8	5.2 ± 3.9[5]	0.61	0.45		
	1	13	21.8 ± 4.5	11.5 ± 6.1	9.3 ± 7.1[3]	0.55	0.47		
	2	14	18.5 ± 3.9	10.8 ± 7.4[4]	11.6 ± 10.6	0.63	0.67		
BDI	3	14	25.0 ± 8.0[2]	11.5 ± 7.2	8.7 ± 6.5[4]	0.44	0.32		
	4	12	25.9 ± 8.6	14.7 ± 11.7[2]	10.7 ± 7.5	0.58	0.44		
	5	15	20.3 ± 5.9	13.9 ± 8.9	10.8 ± 7.7[4]	0.70	0.57		
	1	13	5.3 ± 2.5[3]	2.8 ± 2.4	2.8 ± 2.1[3]	0.60	0.64		
	2	14	4.9 ± 2.3	2.5 ± 2.9[4]	2.4 ± 2.5	0.52	0.60		
BDIadd	3	14	5.1 ± 1.6[2]	2.6 ± 1.9	2.5 ± 1.8[4]	0.51	0.49		
	4	12	6.6 ± 3.2	3.3 ± 2.5[2]	3.3 ± 1.9	0.53	0.57		
	5	15	5.6 ± 2.7	4.1 ± 1.7	3.9 ± 2.7[4]	0.80	0.77		

con = condition; [1] n=10; [2] n=11; [3] n=12; [4] n=13; [5] n=14
1 = Morning/Evening Light; 2 = Evening/Morning Light; 3 = Morning Light (8.00-8.30 a.m.); 4 = Evening Light (8.00-8.30 p.m.); 5 = Afternoon Light (1.00-1.30 p.m.). See text for other abbreviations

Table 2. Mean daily self-ratings

			day →																			
	con	N	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	SD
AMS	1	13	40	41	38	38	36	34	29	25	20	22	21	17	22	23	23	23	19	17	18	14
	2	14	43	41	38	40	38	34	33	30	24	26	25	23	23	26	23	22	24	23	23	14
	3	14	37	34	35	38	34	26	25	23	22	22	25	24	19	16	16	17	16	19	16	12
	4	12	45	46	45	45	42	38	33	28	24	26	23	20	19	20	24	26	21	20	22	13
	5	15	37	32	33	36	28	28	24	22	21	20	21	20	22	25	22	22	20	24	21	14
SSS	1	13	4.0	4.0	3.9	3.8	3.8	3.7	3.1	2.9	3.0	2.8	2.9	2.7	3.3	3.3	3.2	3.1	2.7	2.5	2.4	0.9
	2	14	3.9	3.8	3.5	3.6	3.8	3.5	3.5	3.2	3.4	3.3	3.6	3.2	3.3	3.1	2.9	2.8	3.1	2.9	3.0	1.0
	3	14	4.0	4.0	3.6	4.0	3.9	3.3	3.2	3.0	2.8	2.8	2.8	2.9	2.9	2.5	2.3	2.5	2.6	2.4	2.5	1.0
	4	12	4.4	4.2	4.0	4.6	4.1	3.7	3.6	3.2	3.2	3.3	2.8	3.0	3.2	2.9	3.0	3.1	3.1	3.1	3.1	1.1
	5	15	3.9	3.4	3.7	3.7	3.3	3.3	3.2	3.3	3.2	3.0	2.8	2.7	2.9	3.2	3.2	3.0	2.8	3.0	3.3	1.2
SQ	1	13	7.2	7.5	5.3	6.5	7.2	6.4	4.8	4.1	3.5	4.0	3.9	4.7	5.8	4.0	3.6	3.7	2.3	3.2	3.3	3.3
	2	14	7.2	7.0	3.7	4.3	5.7	5.9	6.1	6.1	4.6	2.6	3.6	4.3	4.1	2.8	3.0	3.6	3.4	3.0	4.8	3.6
	3	14	6.1	7.6	6.2	7.3	7.6	7.2	6.0	5.2	3.9	4.2	3.5	4.8	3.5	2.7	2.0	2.5	1.8	2.9	3.1	3.1
	4	12	7.4	7.0	4.3	5.7	6.1	6.5	6.2	5.0	5.3	4.0	2.4	5.5	4.1	4.7	5.2	5.3	6.0	4.0	4.8	3.3
	5	15	6.2	6.4	4.6	6.0	7.8	4.3	5.2	3.9	2.9	3.4	3.1	4.7	4.5	5.6	5.6	3.9	4.1	3.3	4.9	2.9
VAS depression	1	13	36	36	37	35	35	35	29	28	24	28	29	24	25	29	26	27	25	22	18	23
	2	14	45	47	46	45	44	39	39	34	32	36	36	33	33	33	30	30	27	30	27	21
	3	14	48	48	42	46	38	29	24	23	22	22	26	26	22	18	20	19	20	19	16	19
	4	12	56	58	56	58	50	46	48	39	40	38	28	32	28	31	35	38	30	27	25	26
	5	15	44	42	43	43	40	36	35	30	27	24	22	27	30	34	28	24	26	23	26	22
VAS anxiety	1	13	29	32	25	27	29	27	25	24	20	24	26	21	23	22	21	21	20	16	15	23
	2	14	23	28	24	24	26	20	21	21	20	14	17	22	18	19	19	17	17	18	18	18
	3	14	40	38	32	34	24	17	20	18	17	16	18	17	14	13	16	14	15	11	12	17
	4	12	34	33	26	31	34	25	19	19	18	19	14	13	17	16	15	20	17	14	16	22
	5	15	29	30	26	24	25	22	23	20	15	12	14	20	19	23	20	20	19	19	21	23
VAS anger	1	13	21	18	18	19	21	21	20	18	14	21	16	14	17	17	16	16	16	15	14	27
	2	14	14	17	16	15	17	13	15	14	12	12	11	9	10	12	13	11	12	12	12	13
	3	14	24	14	14	13	9	9	9	10	10	13	9	11	10	7	11	9	9	6	6	11
	4	12	26	27	32	26	24	22	15	14	14	16	10	7	11	15	11	17	13	11	7	21
	5	15	23	20	21	23	19	16	18	12	12	12	11	14	17	15	13	11	14	12	11	17
VAS elation	1	13	31	31	31	33	34	33	43	43	49	43	45	47	47	43	43	44	47	49	48	22
	2	14	31	31	35	31	35	39	38	43	48	44	42	45	42	44	48	52	51	47	51	19
	3	14	34	31	32	30	33	40	44	48	52	47	46	46	46	53	49	51	46	50	50	22
	4	12	21	25	24	22	26	34	28	39	42	39	47	48	50	46	44	44	50	51	49	20
	5	15	31	33	33	29	33	36	38	44	47	47	50	49	45	42	46	45	47	46	45	18
AD-ACL tiredness	1	13	15	16	16	15	15	15	13	13	13	13	13	13	14	14	14	14	13	12	12	3
	2	14	16	15	15	15	15	14	14	13	13	14	13	13	14	13	13	13	13	13	13	2
	3	14	16	16	16	16	16	15	14	14	13	14	14	13	14	13	12	12	13	13	13	3
	4	12	17	17	16	17	16	15	16	14	13	14	13	13	13	13	14	13	13	13	14	3
	5	15	15	14	14	15	14	14	13	13	13	13	12	12	12	13	13	13	12	12	13	3
AD-ACL energy	1	13	9	8	9	10	9	10	11	12	12	12	12	13	11	11	11	11	12	13	14	4
	2	14	7	8	8	8	9	9	9	10	11	11	10	11	11	11	12	12	11	11	12	4
	3	14	9	9	9	8	9	10	10	12	12	12	11	12	12	13	13	13	13	13	13	3
	4	12	6	7	7	7	7	8	9	10	10	10	11	12	11	11	10	11	11	11	11	3
	5	15	9	10	10	9	11	11	12	11	12	12	12	13	12	12	12	12	13	12	12	3
AD-ACL tension	1	13	11	12	11	12	12	12	11	11	10	11	11	10	11	11	10	10	10	9	9	3
	2	14	10	11	10	10	11	10	10	10	10	9	10	10	10	10	10	9	9	10	10	3
	3	14	11	11	11	11	10	10	10	10	10	10	9	10	9	9	10	9	9	8	9	3
	4	12	11	11	11	11	11	10	10	9	10	9	8	9	8	9	9	9	9	9	9	4
	5	15	11	11	10	10	10	10	10	9	9	9	9	10	9	10	9	9	9	9	9	3
AD-ACL calmness	1	13	14	14	14	13	13	13	14	14	15	14	15	16	15	15	15	16	16	16	16	2
	2	14	15	14	14	14	14	14	14	14	15	15	15	15	15	15	15	16	16	15	15	2
	3	14	13	13	14	14	14	15	15	15	15	15	15	15	16	16	15	15	16	16	16	2
	4	12	14	13	13	14	13	14	14	15	15	15	16	16	16	15	16	15	15	15	15	2
	5	15	14	15	15	15	15	15	15	16	16	16	16	15	16	15	15	16	16	15	16	3

con = condition; 1 = Morning/Evening Light; 2 = Evening/Morning Light; 3 = Morning Light (8.00-8.30 a.m.); 4 = Evening Light (8.00-8.30 p.m.); 5 = Afternoon Light (1.00-1.30 p.m.). See text for other abbreviations. SD = Mean standard deviation of the whole period.

All depression scores and nearly all of the remaining self-rated parameters showed a statistical significant main effect of time for all conditions (MANOVA; $p < 0.05$). The only scores that did not reach any level of significance were the improvement in VAS anger scores for the C1, C2 and C3 conditions, AD-ACL-tension scores for C2 and C3, the AD-ACL-calmness scores for C5, and the SQ scores for C2.

The Effects of Timing

All treatment conditions induced a substantial and significant improvement of mood. No significant interaction effects between conditions and time were found (MANOVA) for the majority of the BDI, BDIadd, HRSD and HRSDadd scores in all conditions (for all interaction effects, see Table 3).
In terms of the numbers of patients responding, evening light was the most effective treatment, followed by morning light, but the differences did never reach statistical significance. Thus it may be concluded that the timing in terms of morning, afternoon or evening light does not influence outcome.

The Effects of Rank Ordering Morning and Evening Light

No statistically significant differences in treatment outcome were observed between any pair of conditions (Table 3.). Thus, the effects of evening light following morning light did not differ from the effects of evening light only. Similarly, the effects of morning light following evening light did not differ from morning light only. Furthermore, there were no differences in outcome between the morning light - evening light sequence and the evening light - morning light sequence. In other words, no mutual inhibition or potentiation of treatment modalities was observed.

Prediction

Since the five patient groups showed such similar response patterns, we dealt with the question of response prediction by analyzing the data of the entire patient sample. Unlike our former study (Meesters et al., 1993a), no significant relation between diurnal mood variability and treatment outcome (the difference between pre-treatment and post-treatment

HRSD scores, item 18 (diurnal variation) excluded), was found in this study (Pearson r = 0.07; n=62, P=0.96). We did observe a significant relationship between baseline severity of depression and improvement (n=63, Pearson: r=0.37, p=0.003; Spearman: r=0.37, p=0.003). However, proportional improvement, which takes into account the dependence between the latter improvement score and the baseline HRSD score, did not correlate with baseline severity of depression (n=63, Pearson: r= -0.004, n=63, p=0.98; Spearman: r=-0.014, p=0.91).

Relapse

After light treatment, 38 out of 40 patients who had been treated successfully (final HRSD <8 and at least 50% improvement on day 19), were followed by means of weekly self-ratings (BDI) during the remaining part of the winter until April 15th. Eight subjects relapsed (21%). The mean time-span during which patients who showed no relapse were followed, was 13 weeks (sd $\pm$ 7.0), range 4-26; those who relapsed were followed until their relapse, for a mean duration of 6.5 weeks (sd $\pm$ 2.4), range 3-10. Three subjects (38%) relapsed after the morning light, three (43%) after the evening light, and two (25%) after the afternoon light condition. No patients relapsed after the two cross-over conditions C1 and C2. No statistically significant differences between condition and relapse rate were found.

Table 3. Interaction effects (MANOVA) of the pairwise comparisons of 5 treatment conditions as assessed by means of various rating scales

	BDI	AMS	SSS	SQ	AD-ACL			
					tiredness	energy	tension	calmnes
C1C2								
C1C3								
C1C4								
C1C5				1.72 18,216				1.97 18,450
C2C3	3.69 2,44							
C2C4								
C2C5								
C3C4		2.18 18,342					1.76 18,342	
C3C5	3.94 2,44		1.77 18,378	1.84 18,216				
C4C5		2.40 18,432						

Only significant values ($p < 0.05$) are shown. Upper number: F value, lower number: degrees of freedom. C1 = Morning/Evening Light; C2 = Evening/Morning Light; C3 = Morning Light (8.00-8.30 a.m.); C4 = Evening Light (8.00-8.30 p.m.); C5 = Afternoon Light (1.00-1.30 p.m.). For BDIadd, HRSD, HRSDadd, and all the subscales of the VAS, no significant values were found. See text for other abbreviations

Discussion

The protocol of the application of 30 minutes of 10,000 lux light on four consecutive days resulted in a substantial and significant improvement of mood in all five conditions. There were no statistically significant differences between the five treatment groups in their response to light, nor were any differences found when conditions were compared pairwise. The most likely conclusion is that the timing of light treatment per se is not a critical factor with respect to treatment outcome. Exposures in the morning, in the afternoon and in the evening are all equally effective.

Timing

Direct comparison of the evening, the morning and the afternoon light conditions did not reveal any significant differences. This finding is in line with our previous results where we used light of 2500 lux during 3 hours in the morning and compared it to evening light (Meesters et al., 1993a). Recently, Wirz-Justice et al (1993) have likewise reported no differences in response between morning and evening light. Our findings show that there is no difference between the effects of these latter treatments and those of afternoon light either.

In the light of the phase shift hypothesis (Lewy et al., 1987a) this outcome is unexpected. If phase delay-type patients are more common than phase advanced patients (Lewy et al., 1988a), we would expect better responses in the morning light condition. The relatively small number of patients and the fact that patients were not phase-typed prior to the present study may provide a simple explanation for these findings, however. Furthermore, morning light was administered relatively late in the morning and evening light relatively early in the evening. Earlier timing of morning light (just after waking up) might have resulted in better responses (Lewy and Sack, 1986; Lewy et al., 1987 a; 1987b). It must be noted however, that our morning light responses are of similar magnitude to those obtained in studies with time schedules between 5.30 and 8.00 a.m. (Terman et al. 1989). In addition, even though light application in the afternoon is not supposed to induce a phase shift (Czeisler et al., 1989; Minors et al., 1991) there is still a significant change in mood, similar in magnitude to that after the morning or evening light applications.

Our findings have some theoretical impact on concepts about the origin of SAD and the mechanisms underlying the antidepressant effects of light. Two hypotheses consistent with our findings are the photon counting hypothesis (James et al., 1985) and the supersensitivity hypothesis (Beersma, 1990). These hypotheses are not mutually exclusive. Both attribute a significant role to the total amount of light falling on the retina in a day, irrespective of the time of day at which this occurs.

Besides biological explanations of the therapeutic responses to light treatment, behavioral or psychological explanations may also be relevant. SAD subjects have been found to have personality profiles that differ from those assessed in healthy controls (Meesters, 1992) and in non-seasonal major depressives (Schuller et al., 1993). Moreover, a relationship has

been observed between personality factors and timing of onset of depressive periods in the winter season (Bouhuys et al.,1993a; 1993b). In addition, it has been found that observed behaviour, assessed prior to light treatment, was related to the subsequent responses to light treatment (Geerts et al., 1993).

Predictors

In this study we were not able to replicate our earlier finding (Meesters et al., 1993a) of a significant correlation between diurnal mood variation during baseline and therapeutic response. We have no explanation for this difference other than the difference in sample size (now N=62; previously N=24).
In the present study, a significant positive correlation was found between baseline severity of depression and improvement scores as determined by HRSD delta scores. This significance disappeared when baseline depression was compared with relative improvement. So, the first significant relationship is probably a result of the dependency between baseline HRSD and the improvement score and/or the phenomenon of regression to the mean. Nor were we able to confirm the results of Terman et al. (1989) and Stinson and Thompson (1990), who reported that the therapeutic response of mildly depressed patients was superior to that of more severely depressed subjects. We do not have an explanation for this discrepancy.

Rank order

Rank order within a condition does not appear to have influence on therapeutic outcome either. Rafferty et al. (1990) have postulated that morning light in morning/evening cross-over studies, when administered as the initial treatment to have a dampening or even cancelling influence on the effects of evening light subsequently applied. In the present study, no such effects are found, not when morning light administered immediately before evening light was compared with treatment in the reversed order, nor when it was compared with 4 days of evening light. Nor did we observe a potentiating effect of evening light on subsequent morning light. Therefore, the advantage of morning light as inferred from morning light evening light cross-over designs (Terman et al., 1989) is not confirmed in the present short term rank order study.

The discrepancy may be explained by the differences in design. In a cross-over study, only subjects who have responded successfully to the first treatment and who have had a relapse in the withdrawal period are considered suitable candidates for receiving the second kind of treatment. Subjects who have shown no relapse are excluded from this type of study. In the present study, this was not the case. Subjects contribute to the design irrespective of their response to the first two days of treatment. Therefore, the patient selection of the two study designs differs to a certain extent. Apart from the differences between the patients samples in the studies resulting from this type of selection, there may be other differences as well. The proportion of those experiencing a relapse in the present study is only 21%. In the C2 and C3 conditions there are no patients who experienced a relapse at all. With these figures a cross-over study would not even have been possible.
In view of our findings Rafferty et al's (1990) ideas about the therapeutic significance of diurnal variations of visual adaptation processes (Remé et al., 1990) may also be invalid. If disk shedding and visual sensitivity peak in the morning and the suggested adaptation processes during two days of morning light do in fact take place during two days of morning light, they would not seem to affect the impact of subsequent evening light treatment. However, in cross-over designs, there usually is a time span of one or two weeks between treatment conditions. It is quite possible that the adaptation processes as suggested by Rafferty et al. (1990) take more time than two or three days.

Relapse

Our present data do not provide evidence that the timing of light exposure influences the relapse rate, which was rather low (21%). Besides Meesters et al (1991; 1993b) hardly found any relapses during the remaining part of the winter season when treatment was administered at the very first stage of depression onset. However, in a replication of that study (Terman and Terman, 1993) relapse rates of 71-81% (depending on relapse definition) within 8 weeks after treatment were assessed. Although the relapse rates of the Meesters et al. and the Terman and Terman studies differ greatly, the findings make it clear that the stage of the illness at which light is administered may be crucial for relapse rates and duration of remission. This may be one of the factors causing the low relapse rate of 21% in the present study. It is possible that some patients in the present sample received light treatment at an early stage of their seasonal depression, since we did not record their

clinical state during the interval of the season prior to their entering the design. Another source of variance in the outcome may be the therapeutical setting. We administered light treatment in a hospital setting, whereas patients in other studies are treated at home. Furthermore, we followed the patients quite intensively by assessing their state frequently during the experimental period, and on a weekly basis thereafter. This strategy, while providing a great quantity of useful data on the one hand, may induce strong placebo effects on the other(Eastman 1990; Eastman et al. 1992; Eastman 1993), which may have contributed to the low relapse rates.

Conclusion

In this study we have found similar therapeutic efficacy for light treatment in the morning, the afternoon, and the evening. A sequence of two applications of morning light followed by two applications of evening light revealed similar results, as did the reverse order: morning light followed by evening light. Apart from having implications for possible mechanisms underlying SAD and light therapy, the clinical significance might be that light treatment can be applied at any convenient time of day.

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Chapter V

EARLY LIGHT TREATMENT CAN PREVENT AN EMERGING WINTER DEPRESSION FROM DEVELOPING INTO A FULL-BLOWN DEPRESSION

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Summary

The administration of light at the development of the first signs of a winter depression appears to prevent it from developing into a full-blown depression. Not a single patient from a group of 16 treated this way became severely depressed during the remaining part of the winter season, whereas 5 out of 11 from the non-treated control group did.

Introduction

Seasonal Affective Disorder (SAD), winter type, is a depressive syndrome characterized by the occurrence of depression in autumn and winter, followed by a complete recovery in spring and summer (Rosenthal et al., 1984). Hypersomnia, increased appetite and weight gain are frequent concomitants.

The prevalence of SAD is estimated to be 4.3-10% in Maryland (USA) (Kasper et al., 1989), 4.3% in Iceland (Magnusson et al., 1991), 3.4% in Finland (Hagfors et al., 1992) 2.2% in Switzerland (Wirz-Justice et al., 1992) and 9.2% in Alaska (Booker and Hellekson, 1992). In Japanese outpatient university clinics, SAD was mostly reported in 1-3% of depressed patients who consulted a psychiatrist for the first time (Sakamoto et al., 1992).
In most patients suffering from SAD, the symptoms do not recur every winter (Rosenthal et al., 1984). Without prophylaxis or treatment, about two thirds of the SAD subjects become depressed in the following winter (Thompson, 1989). The depression usually takes from 2 to 6 weeks after the onset of the episode to reach maximum severity (Winton and Checkley, 1989).

The syndrome may well be caused by seasonal fluctuations in light intensity. Several studies have shown that light therapy is a highly effective form of treatment for SAD (Terman et al., 1989).

In the present study, the effects of *early* light treatment on the course of mood during the winter season are investigated. For that purpose, we compared the course of mood in a group of winter depressives who received light therapy at the appearance of the first signs of a depression with that in a control group of winter depressive patients who did not receive any therapy. Preliminary findings of this investigation were presented before (Meesters et al., 1991).

Chapter V

Methods

All participants patients were outpatients meeting the criteria for winter depression as described by Rosenthal et al. (1984). They had been drug free for at least a month (in most cases this was since the previous winter season). In the winters of 1989/1990 and 1990/1991, the subjects' mood was assessed at weekly intervals from September until early April. The self-rating instrument used was the Beck Depression Inventory (BDI, 21 item version; Beck et al., 1961; Beck et al. 1979; Bouman et al., 1985). The BDI contains items to be scored from 0-3. Subjects are allowed to choose more than one answer per item. In those instances, we averaged the scores for that item. To make measurement of the atypical complaints by means of self-ratings possible, we created an addendum to the BDI (BDIadd) in analogy to the addendum to the Hamilton Rating Scale for Depression (HRSDadd; Rosenthal & Heffernan, 1986). This BDIadd correlated highly with the HRSD-Addendum (Meesters and Jansen, 1992a).

The first appearance of a BDI score of $\geq$ 13 was considered to represent the first sign of winter depression. This cut-off score has to be compared to a cut-off value of 17 which Beck et al. (1961) have used for discriminating between no depression and mild depression. The reason for this discrepancy is that most SAD people will not score on the items concerning sleep, eating and weight. So, a score of 13 seems a reasonable criterion of a very mild (beginning) winter depression. Similarly, a score of 22 (instead of 26) was chosen as the cut-off point for severe depression in the SAD subjects in this study.

Patients who reached a BDI score $\geq$ 13 were randomly assigned to either the treatment or the control group. For both groups the number of patients selected in each winter month is indicated in Fig. 1.

Patients completed the following self-rating scales three times a day (7.30 am; 3.00 pm and 11.00 pm) during a subsequent period of 24 days: the Adjective Mood Scale (AMS; Von Zerssen 1986; Elsenga 1988), the Activation Deactivation Adjective Check List, which measures 4 components of activation: energy, tiredness, tension and calmness (AD-ACL; Thayer, 1976; 1978; 1986), a Visual Analogue Scale for depression, elation, anger and anxiety (VAS; Albersnagel, 1988), and the Stanford Sleepiness Scale (SSS; Hoddes et

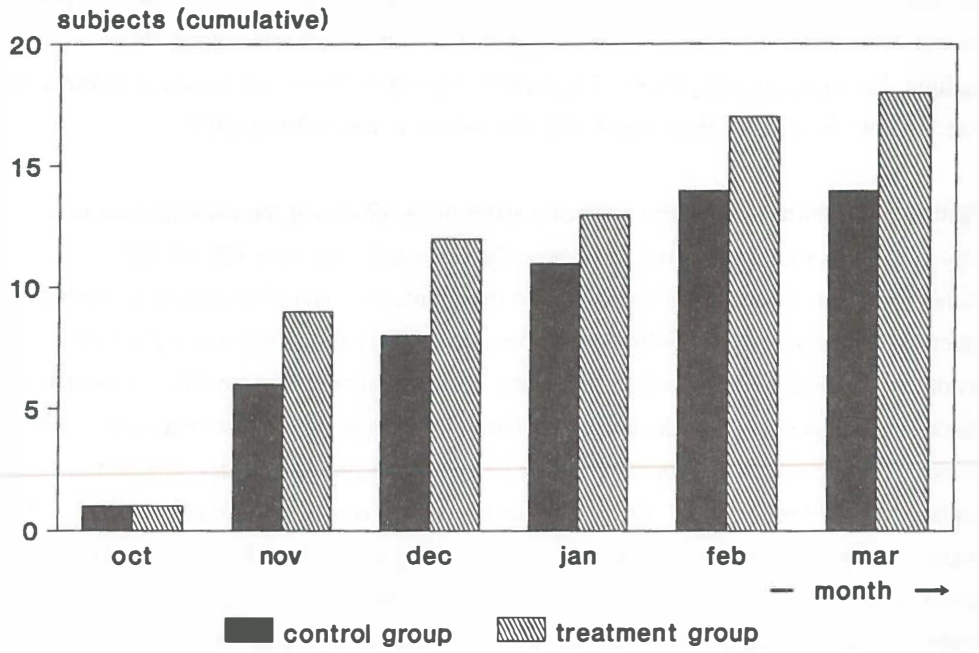

Fig. 1. Cumulative number of subjects who became depressed (BDI $\geq$ 13) during the season, and were assigned to the treatment or the control group.

al., 1973.). The Sleep Quality scale which measures a patient's subjective sleep quality (SQ, range 0-14, with a high score indicating a poor sleep quality; Mulder-Hajonides v.d. Meulen et al., 1980), was completed once a day at 7.30 a.m. and the BDI once a week. After a 4-day baseline period (called 'before'), light therapy was given during a period of 5 consecutive days, from 9.00-12.00 a.m. (this period is henceforth labelled 'during'). The light was produced by a set of four full-spectrum fluorescent light tubes (Philips TL 58 w/95, 2500 lux). Mood assessments were continued during the withdrawal period. This latter period was split into a 10-day period ('after I') and a subsequent 5-day period ('after

II'). At the end of the 'after I' interval, the severity of depression was rated by means of the 21-item Hamilton Rating Scale for depression (HRSD; Hamilton, 1967). The atypical symptoms were assessed by means of seven questions added to the HRSD (HRSDadd; Rosenthal & Heffernan, 1986). Interviewers were members of the research team and who were not blind to the conditions. Taken together, the four periods mentioned above constitute the 'experimental period'. The subsequent part of the winter season is referred to as the 'follow-up period'. Here mood was assessed on a weekly basis (BDI).

Patients in the control group who reached a score of $\geq$ 22 during the experimental or follow-up period were considered to be severely depressed, and were offered light treatment for that reason. Once they received treatment, they served no longer as control subjects in the present study. Subjects who became severely depressed within the first 5 days of the protocol (this is the duration of the baseline period in the treatment group) were excluded from analysis. In such cases a full-blown depression already existed before light treatment, so light treatment could no longer be applied to *prevent* the development of complaints. Fifty-four patients, 10 men, 44 women, were monitored from September onward. Thirty-two subjects were known from previous studies to suffer from SAD (Richter et al., 1992; Meesters et al., 1993). The remaining 22 SAD subjects were recruited through media publicity. All subjects had BDI scores below 13 at the beginning of the study and had no depressive complaints during the part of the winter season before the start of this study.

Thirty-eight participants, all outpatients, (70.4% of the total group) obtained a BDI score $\geq$ 13 and were therefore considered to be developing a depression. Their mean age was 39.1 ($\pm$ 11.5 SD). Twenty of them were given preventive light treatment (4 men, 16 women), the others constituted the control group (5 men, 13 women). The two groups did not differ in severity of depression during the baseline period. Two subjects of the treatment group and four of the control group had a BDI score $\geq$ 22 on day 5 and were excluded from further analysis [2]).
After that, the treatment group numbered 18 subjects and the control group 14 subjects. In

[2]) Eight control subjects and eight subjects in the treatment group in the present analysis participated in our previous preliminary study (Meesters et al., 1991). In that study, three more subjects were included, due to a less strict inclusion criterion.

the experimental period of 24 days, 3 patients from the control group and 2 from the treatment group dropped out, for reasons other than severity of depression (mainly because of the unpleasant obligation of having to perform frequent mood ratings). Patients visited the clinic for light treatment and for the HRSD interviews and completed the self-rating scales at home. As statistical procedures MANOVA with repeated measures, Mann-Whitney U, and the Kaplan Meier survival analysis (Kaplan & Meier, 1958) were used. If subjects, for any reason, dropped out during the experimental period, they were excluded from the MANOVA analysis. However, drop-outs due to the development of a severe depression are relevant to the present study. Their data should be taken into account at least up to the day at which they dropped out. This was done by means of Kaplan Meier analysis. This analysis contains data about the period which started the first week of the experimental period (the week in which the treatment group received light) and which lasted till the end of the season or till subjects dropped out. Each subject participated in this study for one winter season only.

RESULTS

Experimental period

The results are shown in Table 1.

In the treatment condition there was a significant improvement over time ($p = < 0.05$) in all self-rated variables. In the control group there was no improvement at all. MANOVA with repeated measures revealed an interaction effect on almost every self-rated variable (see Table 2.) between the treatment and the control group. Only the tension sub-scale of the AD-ACL merely showed a trend of an interaction effect between both conditions. The mean HRSD score of the treatment group on day 19 (in week 6) was 5.9 ($\pm$ 4.7 SD), the score of the control group 9.1 ($\pm$ 4.9 SD). This difference was not significant (Mann-Whitney U: 82.5, $Z = -1.7$, $p = 0.10$).

Table 1. Average scores of four time intervals of treated vs control subjects

		before day5			during day12			after1 day19			after2 day26		
	cond	N	mean	sd	N	mean	sd	N	mean	sd	N	mean	sd
BDI	contr	14	11.0	5.3	14	12.2	6.1	12	14.0	5.8	11	14.8	10.1
	treat	18	13.7	3.6	18	6.3	5.4	18	5.4	4.8	16	4.7	4.1
BDI addendum	contr	14	3.1	1.9	14	4.0	1.8	12	4.0	3.0	11	4.1	3.2
	treat	18	3.4	1.4	18	1.3	1.1	18	1.1	1.3	16	1.2	1.3
HRSD	contr							14	9.1	4.9			
	treat							18	5.9	4.7			
HRSD addendum	contr							14	7.7	5.1			
	treat							18	3.6	3.2			
AMS	contr	14	24.0	10.2	14	20.2	8.6	14	21.1	10.7	13	23.7	12.4
	treat	18	28.2	9.1	18	19.4	11.9	18	13.9	11.3	18	12.7	9.7
VAS depression	contr	14	92.6	70.0	14	85.5	79.1	14	95.5	102.5	13	105.2	102.6
	treat	18	130.4	66.1	18	93.1	83.3	18	62.5	71.4	18	56.8	68.2
VAS anxiety	contr	14	79.2	89.8	14	74.1	86.9	14	76.9	89.5	13	80.4	85.9
	treat	18	108.2	85.1	18	77.5	68.9	18	54.4	58.0	18	52.8	56.0
VAS anger	contr	14	50.0	87.6	14	46.7	94.8	14	51.8	95.2	13	52.7	98.7
	treat	18	34.3	35.2	18	27.2	32.7	18	17.4	20.2	18	13.7	18.2
VAS elation	contr	14	210.5	76.1	14	211.5	79.9	14	197.1	86.7	13	178.4	84.9
	treat	18	149.9	68.1	18	193.5	87.8	18	236.0	101.1	18	248.5	103.3
AD-ACL energy	contr	14	12.0	2.7	14	12.4	2.8	14	12.6	2.9	13	12.1	3.7
	treat	18	10.6	2.5	18	13.0	2.9	18	14.5	3.1	18	14.7	2.9
AD-ACL tiredness	contr	14	12.8	1.9	14	12.3	1.7	14	12.0	1.8	13	12.8	2.6
	treat	18	14.6	1.8	18	12.7	2.4	18	11.2	2.5	18	11.1	2.8
AD-ACL calmness	contr	14	14.9	1.6	14	15.4	1.9	14	14.9	1.6	13	14.5	1.2
	treat	18	15.3	2.1	18	15.6	1.9	18	16.4	1.7	18	16.3	1.9
AD-ACL tension	contr	14	9.4	2.1	14	9.0	2.3	14	9.2	2.5	13	9.6	2.1
	treat	18	11.0	2.8	18	10.0	2.3	18	9.2	2.7	18	9.2	2.9
SSS	contr	14	3.3	0.6	14	3.0	0.5	14	3.0	0.6	13	3.2	0.8
	treat	18	3.5	0.7	18	2.9	0.8	18	2.5	0.9	18	2.5	1.0
SQ	contr	14	4.9	2.2	14	4.9	2.0	14	4.4	1.9	13	4.6	2.9
	treat	18	5.5	1.7	18	4.0	1.8	18	3.1	1.8	18	2.7	2.2

CONTR= Control group; TREAT=Treatment group; BDI=Beck Depression Inventory; AMS=Adjective Mood Scale; VAS=Visual Analogue Scale; AD-ACL=Activation Deactivation Adjective Check List; SSS=Stanford Sleepiness Scale; SQ=Sleep Quality scale

Table 2. Interaction effects between treated/control subjects and time

MANOVA	INTERACTION		
	F	df	p
BDI	10.64	3,72	0.00
BDI addendum	10.11	3,72	0.00
AMS	6.76	3,87	0.00
VAS depression	5.00	3,87	0.00
VAS anxiety	3.33	3,87	0.02
VAS anger	2.80	3,87	0.04
VAS elation	8.66	3,87	0.00
AD-ACL energy	7.18	3,87	0.00
AD-ACL tiredness	6.10	3,87	0.00
AD-ACL calmness	3.14	3,87	0.03
AD-ACL tension	2.26	3,87	0.09
SSS	3.36	3,87	0.02
SQ	3.71	3,87	0.01

BDI=Beck Depression Inventory; AMS=Adjective Mood Scale;
VAS=Visual Analogue Scale; AD-ACL=Activation Deactivation Adjective Check List;
SSS=Stanford Sleepiness Scale; SQ=Sleep Quality scale

Follow-Up

After the experimental period of 26 days the patients were followed by means of weekly BDIs until the beginning of April. Five control subjects became severely depressed (BDI$\geq$22) during the experimental period or after. They were therefore given light treatment and did no longer contribute to the design.

In contrast, not a single patient of the treatment group ever exceeded the BDI value of 22, so severe depression was not observed in this group. Kaplan Meier Survival Analysis revealed a significant difference between the two groups in developing a severe winter depression (Chi-square: 8.98; df=1; p=0.0027).

During the experimental period and the consecutive follow-up period some subjects in both the treatment and the control group became mildly depressed (BDI $\geq$ 13 and < 22) for one or more weeks. On calculating the ratio of the number of weeks in which subjects reached a BDI score $\geq$ 13 and the total number of weeks of the recording period, we found 0.14 $\pm$ 0.24 for the treatment group and 0.45 $\pm$ 0.35 for the control group. This difference is significant (Mann-Whitney U: 55.0, z= -2.7, p=0.007). Fig. 2. shows the course of mood of the two groups during the winter season after the first onset of depression.

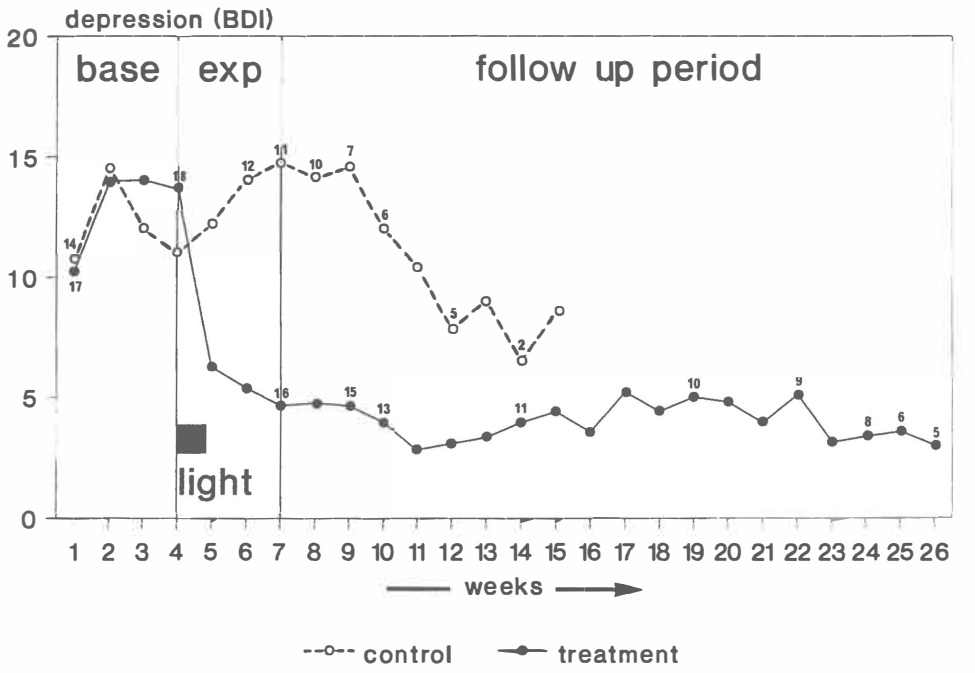

Fig. 2. The course of mood (Beck Depression Inventory) in the treated group (n=18) and the control group (n=14). Numbers of individuals contributing to the data are indicated. Data are synchronized with respect to the 24-day experimental period. Base = baseline period; exp = experimental period; light = light treatment for the treatment group. The gradual reduction of the number of subjects in each group is explained in the text.

Two of the severely depressed patients in the control group recovered after one series of 5 days of light treatment, two patients needed two series, and one did not recover at all in response to light. In addition, none of the 4 subjects who dropped out of the control group and who had successful treatment became severely depressed during the same winter season. Fig. 2. shows that the number of patients decreased over time in both groups. This effect can partly be attributed to the different points in time at which patients entered the study: Since the end of the experiment was set at the beginning of April, the duration of the monitored time intervals varied considerably. In addition, the reduction of patients in the control group is also partly caused by the drop-out due to the severity of depression.

Discussion

The administration of light at the very first signs of a winter depression, evidently prevented it from developing into a full-blown depressive episode. The treatment improved mood, the level of subjective activation and sleep quality. The control group of patients, who had not been given any therapy, either showed a deterioration or no change of depressed mood. This is illustrated by all mood variables examined [3]).

The BDI scores suggest that, in general, the beneficial effects of light treatment were maintained until spring. Only a minority became mildly depressed again, and this lasted at most for only a few weeks. Not a single person of the treatment group became severely depressed in the part of the winter season after light treatment. This finding is at variance with the reported relapse period of 3-4 days (Rosenthal et al., 1985a; Rosenthal et al., 1985b; Terman et al., 1989). However, several authors have found no such fast relapses. Wehr et al. (1986) reported that five out of seven patients did not relapse completely to their baseline depression levels before they started a second treatment condition within 9 days. Yerevanian et al. (1986) found virtually no relapse and Grota et al. (1989) no relapse at all within a period of 14 days after treatment. Wirz-Justice et al. (1986a) described a

[3]) A quantitative comparison of the results of the present analysis and the published preliminary analysis (Meesters et al., 1991), may give the impression that the increased number of subjects has substantially reduced the magnitude of the overall effects. This, however, is not the case. In the preliminary analysis, data of all subjects from the two groups after admission to the experimental period were taken into account, including those subjects who had a BDI $\geq$ 22 score on day 5. This selection fully accounts for the differences.

case study of a patient who had no relapse up to 3 months after treatment. In another study, Wirz-Justice et al. (1986b) reported that the time interval between termination of treatment and relapse showed extreme variation: some patients relapsed within 1 day, others remained free of symptoms during the remaining part of the winter. Meesters et al. (1993) found a relapse rate of 54% within the same winter season after a successful treatment (with the relapses occurring in a period from 2 to 14 weeks after treatment). In that study, 46% of the subjects didn't relapse in a period of 9-21 weeks after treatment (the remaining part of the winter season; the average period being 14,7 weeks).
Lasting remission was also noted for the 4 subjects from the control group, who had been successfully treated, after a BDI score $\geq$ 22 had been reached. We have no explanation for the differences between the studies. Perhaps the weekly contact of the subjects with the research centre (through sending self-rating scales) contributed as a placebo effect to the lasting remission (Eastman, 1990).

However, whereas treatment at the onset of symptoms seems to prevent the development of a full-blown winter depression, we have shown in a separate study that winter depression cannot be prevented by exposing SAD patients to light early in the winter season when there are no complaints yet (Meesters et al., 1992b). This discrepancy suggests that the precise timing of light therapy is of great significance to the therapeutic effects. Light therapy administered at the emergence of the first depressive symptoms has prophylactic effects, whereas its administration in a symptomless phase, long before, has not. Variations in timing may therefore explain differences in relapse rates between studies.

In interpreting our data, there is a point which has to be mentioned. Not only did the treatment condition imply the administration of light, but it also included visits to the clinic on 5 consecutive mornings. In contrast, the control patients carried on with their normal daily routines. Consequently, the conditions differ at least in these two aspects. Without proper control for these differences, it remains uncertain what factors are responsible for the beneficial effect of the treatment condition.

Yet, in the prolonged follow-up period, contacts with the clinic were similar for both patient groups. Therefore, it is obvious from our data that a one-week period of light treatment, with all of its accompanying physiological and psychological aspects, when

applied at the very first signs of a winter depression is sufficient to reduce these minor complaints and to prevent the development of a severe winter depression for a long period of time.

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Chapter VI

AN ATTEMPT TO PREVENT WINTER DEPRESSION BY LIGHT EXPOSURE AT THE END OF SEPTEMBER

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Introduction

Seasonal affective disorder (SAD), winter type, is characterized by the occurrence of depression in autumn / winter, followed by a complete recovery in spring / summer. In SAD patients, some atypical symptoms are highly characteristic, such as hypersomnia, carbohydrate craving, weight gain, fatigue and loss of social interactions (Rosenthal et al., 1984).

The repeated occurrence of symptoms during successive winters is one of the diagnostic criteria. Not every SAD patient becomes depressed every year, however. In prospective studies it was found that 70.4% of the SAD diagnosed subjects who were followed from a symptom-free moment at the end of September, became depressed during the following winter (Meesters et al., 1991, 1993a).

In a previous study it was found that severe winter depression can be prevented by light treatment administered at the first signs of an emerging winter depression, that is, the moment subjects reported complaints of slight depression (Meesters et al., 1991, 1993a). In the present study, the question was raised whether light exposure given at the beginning of the winter season, when subjects are still free of symptoms, could be successful in preventing the development of a winter depression during the rest of the season. Such a treatment, which might prevent depression altogether, would be highly advantageous.

Methods and Results

Fifteen SAD patients, all diagnosed according to the criteria of Rosenthal et al. (1984) gave their consent to participate in the study. They had been drug free for at least one month prior to the study, were without physical complaints, and had reacted with a full remission to light treatment in the previous winter season. They received light exposure in the clinic (2500 lux, Philips TL 58 w/ 95). The end of daylight saving time (Central European Time, September 29, 1991) fell within the time schedule of the study. Light exposure was administered at the same time in the natural light/dark cycle for all patients, that is, for 5 patients from 10.00 am till 1.00 pm before the change of the clocktime and for 6 patients from 9.00-12.00 am after the time change. In this way the timing of light treatment

equalled that used in our previous 'prevention' study (Meesters et al., 1991; 1993a). The course of mood was assessed every week during the entire winter season from the September 7, 1991 through the April 15, 1992 by means of the Beck Depression Inventory (BDI, 21-item version)(Beck at al., 1961; 1979; Bouman et al., 1985). In analogy to the addendum to the Hamilton Rating Scale for Depression (Rosenthal & Heffernan, 1986), we created an addendum to the BDI (BDI-ADD), in order to assess atypical symptoms by means of self-ratings (Meesters and Jansen, 1993b). This addendum contains the items 12 (social withdrawal) and 17 (fatigue) from the BDI, and the inversely formulated items 16 (hypersomnia), 18 (appetite) and 19 (weight gain).

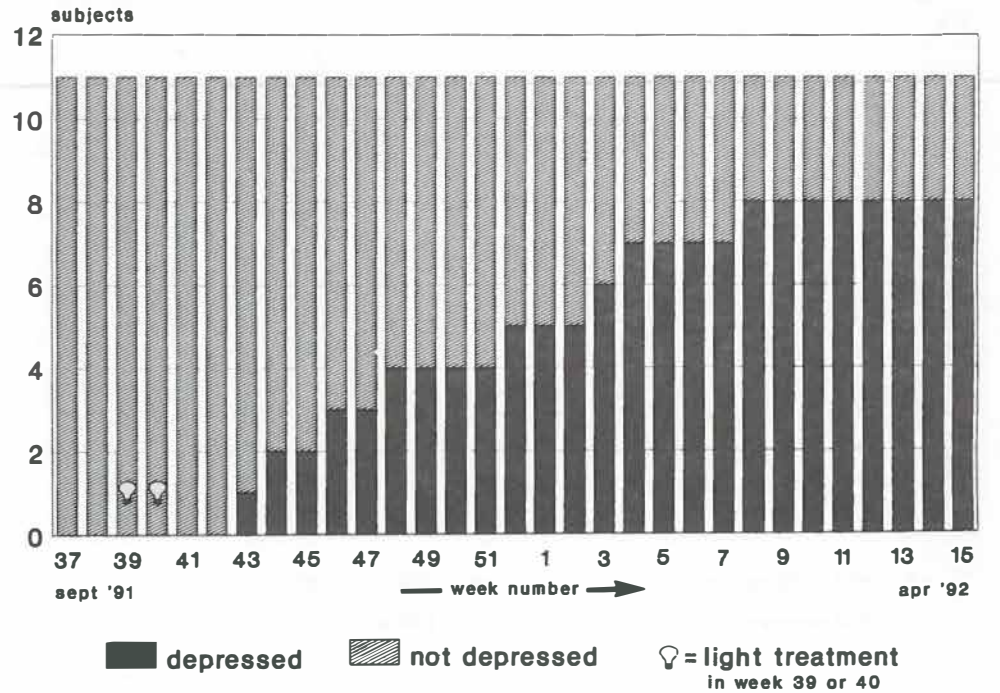

Fig. 1. Cumulative number of subjects who became depressed (2 consecutive scores on the Beck Depression Inventory (BDI) $\geq$ 13, or a score of BDI $\geq$ 22) during the season after an initial light treatment at the end of September. At that time subjects were free of symptoms.

There were four drop-outs: two subjects showed signs of depression before light treatment was started and two other subjects did not complete the design because of the unpleasant obligation of having to perform weekly mood ratings. Therefore, data from 11 subjects were available for analysis, 1 man, age 36, and 10 women, mean age 37.7, sd $\pm$ 9.9. As an inclusion criterion we used a score on the BDI $<$ 13, during the two weeks before light exposure. After light exposure, subjects completed the BDI at home and sent it to the clinic. If they reached a BDI score $\geq$ 22 at a particular moment, or a BDI score $\geq$ 13 for two consecutive weeks, they were considered to be depressed and were therefore offered light treatment. Eight out of eleven subjects (= 73%) reached this criterion. Fig. 1. shows in which month the subjects became depressed.

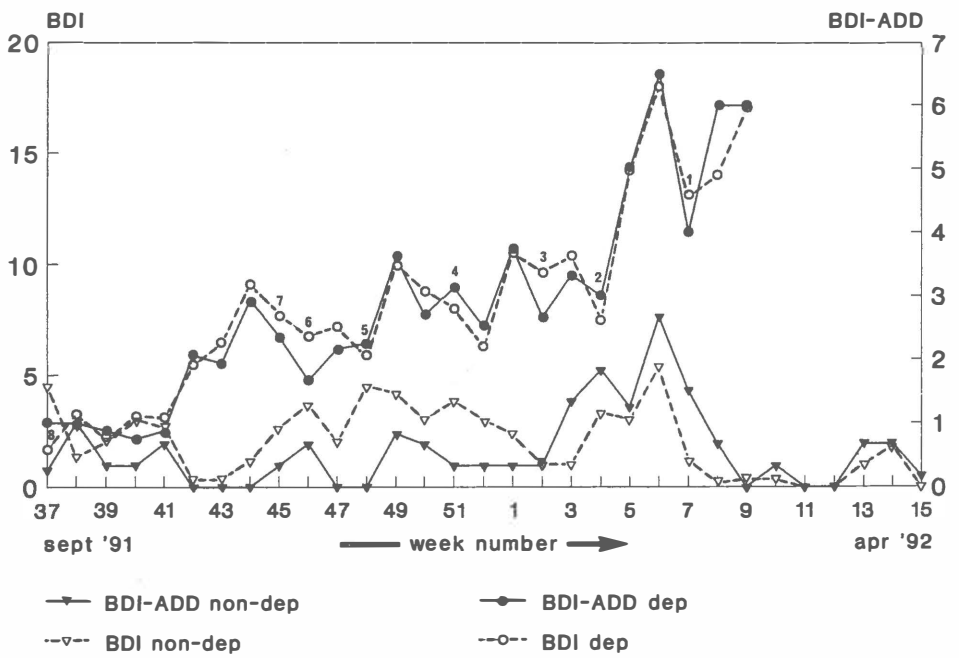

Fig. 2. The course of mood (Beck Depression Inventory, BDI) and the course of atypical symptoms (Beck Depression Inventory - Addendum, BDI ADD) during the winter season. Non-dep: subjects who did not become depressed (N=3); Dep: subjects who became depressed. Numbers of individuals contributing to the curve are indicated for the depressed group. The reason for the decreasing number of subjects as time progressed in the depressed group is that subjects were removed after they became depressed, and therefore got light treatment.

The time interval between the initial treatment, at the end of September, and the development of depression varied from 2 to 19 weeks (mean 9.6 weeks).

The course of depression and the course of atypical complaints are shown in Fig. 2., both for the group of subjects that reached the criterion for depression and for the group that did not. Obviously, light exposure early in the winter season did not prevent the occurrence of depressive episodes. The time course of depression is very similar to the time course of atypical complaints in both groups.

For all 11 subjects, significant correlations ($p = < 0.05$) between individual BDI and individual BDI-ADD scores were found (range Pearson R: 0.464 - 0.983; range n: 8 - 31). After removing the items 12, 16, 17, 18 and 19 from the BDI, because of their dependency with the BDI-ADD scores, the correlations between the remaining part of the individual BDI and the individual BDI-ADD scores are still significant ($p = < 0.05$; range Pearson R: 0.509 - 0.976). Using BDI-ADD scores $\geq$ 4 for two consecutive weeks as a criterion for the incidence of a depressed period, there was 100% correspondence between the criteria based on the BDI and those based on the BDI-ADD.

Discussion

An attempt to prevent the development of winter depression by light exposure at a symptom-free period at the beginning of autumn was not successful. The percentage of subjects who became depressed (73%) was comparable to that found by Thompson (1989), who reported that 67% of the SAD subjects diagnosed in the summer became depressed during the following winter and by Meesters et al. (1993a) who reported that 70.4% of SAD diagnosed patient became depressed when they were followed from a symptom free period (summer). It is hard to tell whether this light treatment had any delaying effects on the course of depression, as no control group was studied. Two subjects reported spontaneously that the beginning of their depression was substantially later in the season, as compared to their experiences from the previous winters. Moreover, the possibility cannot be ignored that exposure to more light (longer, higher intensity) or to light exposure at other moments of the day may have had the effect of preventing a depressive episode.

The present results differ substantially from the results of a previous study (Meesters et al., 1991, 1993a). There it was found that the development of a full-blown winter depression could be prevented by light treatment applied at the first signs of depression. In contrast to

the present study, no severely depressive episode was observed during the remaining part of the season. If the effects of this study can be replicated in future studies, these discrepancies may perhaps be explained from state-dependent sensitivities to light treatment; at the first seasonal occurrence of symptoms patients could still be very sensitive to light treatment, whereas a complete recovery may be more difficult to achieve when a depression has persisted for a longer period of time. This hypothesis might also explain why studies vary considerably in the rate of relapse. Wether this is related to the phase in the depression episode at which light treatment is applied, needs further investigation.

Acknowledgment

We are grateful to J.S. Borger for her improvement of the English used in this article.

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Chapter VII

CONCLUDING REMARKS

In this thesis, several light treatment designs have been compared with the aim to specify the optimal timing of light treatment in terms of time of the day, and timing of onset of a new episode. Those light treatments that were applied *during* the illness, were very effective; rapid and highly significant improvement was observed in the course of one or two weeks after treatment onset. Treatment *prior to* the illness turned out to be ineffective. The practical and theoretical consequences of these findings will be discussed briefly.

Timing during the day

Exposure to 2500 lux

In Table 1. the results of the studies in this thesis are compared to the pooled data in the classic review of Terman et al. (1989).
In the Groningen studies, no statistically significant differences were found between treatment outcome after morning and evening light. Our results after the morning light condition are similar to those reported in the review by Terman et al.. The effects of evening light seem more favourable in our studies, however, than in those reported by Terman et al. (1989). This discrepancy may be due to differences in sample sizes. Ours was small as compared to those in Terman's review. Rank-order effects in the cross-over studies reviewed by Terman et al (1989) may also be responsible, however. In a recent study by Wirz-Justice et al (1993) employing a similar parallel design, no statistical differences were found either.

Exposure to 10,000 lux

In our last study (Chapter IV) the effects of light with an intensity of 10,000 lux applied at three different times of day were assessed (morning, afternoon and evening). In addition, light was administered in two different short-term rank orders. Treatments were given in a parallel design. No statistically significant differences in outcome were found. Although no direct comparisons were made, the data suggest that light with an intensity of 10,000 lux during 30 minutes is therapeutically superior to light of 2,500 lux during 3 hours. A similar suggestion was formulated by Terman et al. (1991), who remarked that

the two 10,000 lux studies known at that moment belonged to the list of studies with the strongest clinical effects. In view of these considerations, a 10,000 lux treatment of 30 minutes a day is to be preferred to a 2500 lux treatment of 3 hours a day.

Table 1. Treatment outcome across Light Therapy Studies (Terman et al., 1989) and the studies from this thesis

	N	Baseline HRSD	Treatment HRSD	Proportion showing HRSD decrements post treatment		
Light exposure condition				-50%	< 8	-50 %, < 8
Morning light alone	172	17.8	8.1	0.66	0.56	0.53
Morning light alone Groningen*	14	18.1	8.9	0.64	0.57	0.57
Morning light alone Groningen**	13	16.9	4.7	0.85	0.69	0.69
Midday light alone	34	21.2	12.4	0.50	0.32	0.32
Midday light alone Groningen*	14	15.9	8.4	0.57	0.57	0.57
Evening light alone	143	18.0	10.1	0.50	0.43	0.38
Evening light alone Groningen*	10	16.1	7.1	0.60	0.50	0.50
Evening light alone Groningen**	10	17.5	5.5	0.90	0.80	0.80
Morning + Evening light	136	21.1	9.2	0.68	0.52	0.51
Evening / Morning light Groningen*	14	16.2	8.2	0.50	0.50	0.50
Evening / Morning light Groningen**	13	19.0	6.5	0.75	0.67	0.67
Dim-light control	77	23.4	20.0	0.21	0.13	0.11

* data from 1989/1990; ** data from 1990/1991, 1991/1992, 1992/1993: 10,000 lux light treatment. Other studies applied 2500 lux light intensity.

In our study, we find a significant improvement after afternoon light, which is not statistically different from treatment outcomes after morning or evening light. Compared to the pooled data by Terman et al. (1989), our results after midday light seem to be better. The Terman data about midday light treatment are based on three studies, however, showing large variation in treatment outcome figures. One of them presents results in terms of proportional improvement comparable to those of our study (0.57) (Hellekson and

Rosenthal, 1986; HRSD -50%, <8: 0.57; N=7). In the second study (N=11) by Isaacs et al. (1988) the proportional improvement is 0.45. The third study (N=16) by Jacobsen et al. (1987) shows a proportional improvement of 0.13. Obviously, the last study, as it had the largest number of participating subjects, had the greatest influence in the pool. In view of these data, the discrepancy between our results and those presented in Table 1. is much less pronounced than the figure suggest.

As discussed before, the small sample sizes and a possible rank order effect may be responsible for differences in the outcome of studies. Our conclusion based on our data must be that timing on the day of light treatment has no influence on treatment outcome. As shown in chapter IV, differences in short-term rank order of light exposure are probably also unimportant.

Timing of light treatment in relation to the onset of a new depressive episode

SAD is a recurrent illness by definition. The timing of the onset of the depressive episodes is fairly predictable, which gives the opportunity to prevent them. In connection with this, two experiments were performed. In one study, we found evidence that light treatment at the end of the summer, in the absence of any complaints, does not prevent depression during the subsequent autumn and winter (chapter VI), whereas light treatment administered when the first signs emerge does. It successfully prevents the development of a severe depression (BDI$\geq$22) during the remaining part of the winter season, as is shown in chapter V.

Terman and Terman (1994) were not able to replicate these results. Although their patients relapsed much later than usual after a successful treatment, most of them in fact did relapse. After treatment shortly after the onset of the symptoms, the average relapse score for 15 subjects was just over 4 weeks, whereas, in other studies, most of their patients, who had been treated when having a full blown-depression, relapsed usually within a week. A mere 25% of Terman's patients did not relapse within 8 weeks under our criterion of a mild depression (BDI$\geq$13). In this study, no data on the further development of depression were available since the patients were allowed to resume light treatment after reaching a BDI $\geq$ 13 score. Some subjects in our study, both the treatment and the control groups

reached a BDI $\geq$ 13 and < 22 for one or more weeks, but the ratio between the number of weeks in which subjects reached such a score and the total number of weeks of the recording period was significantly lower for the treatment group. In the Terman study, there was no control group. Another difference between the two studies might be that all subjects in the Terman study had shown a positive clinical response to light treatment in previous years and that all of them relapsed within 3 weeks of withdrawal (mostly within 1 week). In our study, subjects had not been selected on those characteristics. Nevertheless, the discrepancies between the two studies cannot be fully explained, even if some differences in methodology have been accounted for. On the other hand, the studies seem to agree with respect to the importance of the timing of light treatment relative to the individual seasonal course of the illness.

In this context the phenomenon of relapse should be discussed. Relapse after treatment is much more common in the studies from the USA than in those from Europe (see Chapter IV for a discussion). These discrepancies may be explained partly by differences in timing of treatment relative to the onset of the next depressive episode. Differences in relapse rates in our own studies may illustrate this suggestion. In our first study (Chapter III) we found a relapse rate of 54%, in the last study (Chapter IV) this percentage was 21. In contrast to the first study, the last study was partly carried out with subjects who had participated in previous studies. Furthermore, in a larger number of participants the diagnosis SAD had been assessed in summer, i.e. in their asymptomatic period instead of during their depressive episode. They were known as SAD patients and their state was assessed by means of self-rating instruments on a weekly basis from September onwards. It is likely that in the last study patients were treated at an earlier stage of their winter depression than in the first study, and therefore showed fewer relapses.

Theoretical Implications

The comparison of the effects of light treatment in the morning with the effects of light treatment in the evening has been inspired by the phase shift hypothesis (Lewy et al., 1987). In both our studies, examining the effects of timing of light treatment during the day, the results were inconsistent with this hypothesis. Outcomes after morning, afternoon and evening light treatment were not statistically different. As discussed in chapters III and

IV, we have to conclude that the phase shift hypothesis is unable to explain why light exposure is beneficial in SAD. This opinion is in line with Rosenthal and Wehr's (1992) more general conclusion: "At this moment there is no satisfactory explanation of the mechanism of SAD and its response to light treatment, which meets sufficient empirical support."

Although current chronobiological explanations seem insufficient at present, chronobiological factors might still be involved in the response to light treatment. This assumption is based on the observed importance of the timing of light treatment in terms of the individual seasonal course of the illness. Although Terman and Terman did not confirm our results completely, their data too indicate that early timing of light is beneficial (Terman and Terman, 1994). Since light treatment prior to the development of an SAD episode does not elicit any detectable beneficial effect on the course of mood in the subsequent autumn or winter, it is conceivable that light/dark ratio specific to the individual triggers the development of the disorder, and that at this particular time the most powerful effects of light treatment can be obtained.

In spite of the speculative nature of these considerations it seems plausible that chronobiological explanations for our findings might be meaningful. On the other hand, the placebo effects of light treatment (Eastman, 1990; 1993) cannot be ruled out. Psychological explanations for the beneficial effects of light treatment are still possible. In this context differences in personality profiles between SAD patients and normal subjects (Meesters, 1992) and between SAD patients and non-seasonal major depressives (Schuller et al., 1993) should be mentioned. It may well be that personality traits decide whether mood disordered patients benefit from light exposure or not. It has been shown besides that certain types of behavioral processes in the interaction between patient and environment might play a role in the therapeutic mechanisms (Bouhuys et al., 1994a, 1994b; Geerts et al., 1993). Clearly, multidisciplinary research is needed to unravel the mechanisms involved in SAD.

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Chapter VIII

SAMENVATTING

Onder winterdepressie verstaan wij een conglomeraat van klachten, die beginnen in het najaar of de winter en in het voorjaar of de zomer weer verdwijnen. De klachten bestaan doorgaans uit somberheid, moeheid, lusteloosheid, concentratieverlies en libidoverlies. Naast deze voor alle depressies kenmerkende symptomen komen bij de winterdepressie vaak een aantal a-typische symptomen voor: een grotere slaapbehoefte, een toename van de behoefte aan eten, met name van calorierijk voedsel, en gewichtstoename. Deze vaak jaarlijks terugkerende klachten zijn goed te behandelen door blootstelling aan intens helder kunstlicht. In dit proefschrift zijn een viertal klinische studies beschreven waarin verschillende behandelingen worden vergeleken. De implicaties van de onderzoeksresultaten voor de behandelpraktijk en voor ons begrip omtrent de achtergronden van het ontstaan van winterdepressies en die van de werkzaamheid van het licht worden bediscussiëerd.

In de studies wordt het verloop van de toestand van de patiënten over lange perioden vervolgd. Dit betekent dat hun toestand veelvuldig vastgesteld diende te worden. Een klinisch interview is voor deze vaststelling weliswaar zeer geschikt, maar het is zowel voor de onderzoeker als de patiënt te tijdrovend voor frequente toepassing. Zelfbeoordeling is geschikter. Omdat de bestaande zelfbeoordelingsschalen voor depressies niet zijn toegesneden op de speciale kenmerken van winterdepressies (de atypische klachten) werd de meest gebruikte zelfbeoordelingsschaal (Beck Depression Inventory, BDI) uitgebreid en deze uitbreiding geëvalueerd. Bij 76 winterdepressieve patiënten in hun depressieve periode werden zelfbeoordelingsscores vergeleken met de resultaten van een internationaal gebruikelijk semi-gestructureerd interview. Gezien de zeer hoge correlatie tussen de resultaten van beide methoden kan de zelfbeoordeling als een verantwoord alternatief worden beschouwd voor het klinische interview.

De vier klinische studies van dit proefschrift betreffen twee thema's.

I. Als eerste werd onderzocht op welk moment van de dag het licht het meest effectief is. Dit onderzoek werd geïnspireerd door de zogenaamde fase verschuivingshypothese die poneert dat er bij mensen die lijden aan winterdepressie sprake is van een abnormale fase relatie tussen een aantal lichamelijke processen met een circadiaan ritme (bijvoorbeeld

de temperatuur of de aanmaak van melatonine) en het slaap/waak ritme. Bij de meeste mensen die aan winterdepressie lijden zou er sprake zijn van een verschuiving van de fase van de circadiane ritmen naar een later tijdstip. Volgens de genoemde hypothese zou deze verschuiving ongedaan worden gemaakt door blootstelling aan licht in de ochtend, terwijl dat in de avond geen of zelfs averechts effect zou opleveren. Eerdere studies door andere onderzoekers leverden tegenstrijdige resultaten op, die zowel voor als tegen de hypothese pleiten.

De eerste studie van dit proefschrift, waarin de effecten van licht in de ochtend met die van licht in de avond werden vergeleken, leverde geen statistisch significante verschillen in therapeutische uitkomsten op. De toestand van beide groepen patiënten was na afloop van de lichttherapie in gelijke mate verbeterd ten opzichte van die voor de behandeling. In dit onderzoek bestond de behandeling uit blootstelling aan helder wit licht op 5 opeenvolgende dagen gedurende 3 uur. De lichtintensiteit was 2500 lux.

In de tweede studie werd licht gebruikt van 10.000 lux gedurende 30 minuten op 4 opeenvolgende dagen. Vijf groepen patiënten kregen verschillende behandelschema's aangeboden: licht in de ochtend, de middag, de avond, twee dagen licht in de ochtend gevolgd door twee dagen licht in de avond, en de omgekeerde volgorde. Ook hier werden geen statistisch significante verschillen in therapeutische effecten van de diverse behandelingen gevonden.

De fase verschuivingshypothese vindt in ons onderzoek dus geen empirische ondersteuning. Ook het door sommige onderzoekers gesuggereerd belang van de rangorde van de behandeling (ochtend lichtbehandeling zou een volgende avondlichtbehandeling ongunstig beïnvloeden) kon niet worden vastgesteld. Op grond van het beschreven onderzoek lijkt de conclusie gerechtvaardigd dat het voor het therapeutisch effect niet uit maakt of de behandeling in de ochtend, de middag of de avond wordt gegeven en dat de volgorde binnen een behandeling met afwisselend ochtend- en avondlicht evenmin therapeutische consequenties heeft.

II. Ten tweede werd onderzoek gedaan naar het optimale moment van behandeling in termen van het verloop van de stoornis binnen het seizoen. Winterdepressie keert per definitie vaak jaarlijks binnen een bepaalde periode terug. Het ligt dan ook voor de hand dat dit gegeven aanknopingspunten kan bieden voor preventie. In dit kader werden twee onderzoeken gedaan.

Iemand die lijdt aan winterdepressie krijgt daar niet ieder jaar last van. In de eerste studie werden de preventieve mogelijkheden onderzocht bij die patiënten die tekenen vertoonden dat zij wellicht wel een depressie zouden gaan ontwikkelen. Zij werden opgespoord door een grote groep patiënten vanaf hun klachtenvrije zomer middels wekelijks door hen in te vullen stemmingsvragenlijsten te volgen. Zodra de eerste klachten zich voordeden werd de betreffende patiënt toegewezen aan één van twee groepen: een behandelgroep of een controlegroep. De behandelgroep werd volgens het gebruikelijke therapeutische protocol 5 dagen blootgesteld aan 2500 lux gedurende 3 uur. De controlegroep werd onbehandeld vervolgd en kreeg pas lichtbehandeling zodra er sprake was van een duidelijke depressie. Het bleek dat mensen die vroegtijdig lichttherapie kregen aangeboden gedurende de rest van het winterseizoen geen ernstige depressie ontwikkelden. Slechts in enkele gevallen werden enige lichte klachten gedurende het verloop van de winter gemeld. De terugval is aanzienlijk geringer dan bij patiënten die "klassiek" behandeld worden, d.w.z. als de depressie zich al duidelijk ontwikkeld heeft. De onbehandelde controlegroep werd in grote meerderheid ernstig depressief en kreeg daarvoor een lichtbehandeling aangeboden. Het verschil tussen beide groepen was statistisch significant.
In de tweede studie werd bij een groep winterdepressieve mensen die in voorgaande winters positief op lichttherapie hadden gereageerd aan het begin van de herfst lichttherapie aangeboden op een moment dat er nog geen klachten waren. De resultaten uit dit onderzoek lieten zien dat een dergelijke behandeling geen positieve effecten opleverde. Er werden ongeveer evenveel patiënten depressief als in voorgaande jaren.

De klinische conclusie is dat lichttherapie effectief is. Het uur van toediening lijkt geen rol te spelen bij effectiviteit. Wat wel van belang voor het effect lijkt, is de fase waarin ingegrepen wordt. Lichttherapie op een moment dat de winterdepressie zich begint te ontwikkelen blijkt in staat ernstig depressieve klachten gedurende de rest van het winterseizoen te kunnen voorkomen. De gebruikelijke behandelstrategie (lichttherapie als de depressie zich volledig ontwikkeld heeft) levert meer terugval op en noopt dus dikwijls tot herhaalde behandelingen.
De theoretische conclusie is dat voor de gepostuleerde chronobiologische afwijkingen geen steun werd gevonden.

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